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California Medicine

VOLUME 110 · NUMBER 1

January 1969

ANNUAL SESSION ISSUE

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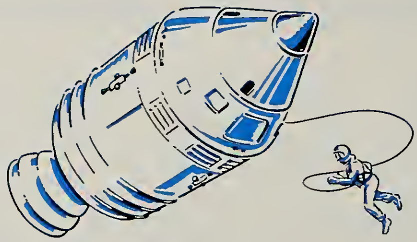

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Multiple Myeloma

Clinical Correlation of Immunoglobulin Changes With Therapy— A Report of 23 Cases

CHRISTA M. BASCH, M.D., AND ERNEST H. ROSENBAUM, M.D., *San Francisco*

■ *Twenty-three patients with multiple myeloma were studied. They were grouped according to their clinical response and changes in myeloma globulin in the serum or urine while under chemotherapy. Sixteen responded favorably with clinical improvement and marked reduction in the respective M-globulins. Four did not respond and showed progression of disease, and three had short-lived clinical response with essentially unchanged myeloma-globulin values. Patients with renal insufficiency showed simultaneous improvement of uremia and M-globulins in response to chemotherapy.*

Three patients had solitary plasmacytomas when first seen, and dissemination occurred later in one.

Combination of alkylating agents with steroids appeared to give faster, longer-lasting and more satisfactory clinical remissions, although the bone marrow may remain essentially unchanged. Radiation therapy was the most effective agent against localized pain (without altering the M-globulin) when used alone. Twenty-two of the 23 patients already had a significant decrease in IgM at the time multiple myeloma was diagnosed. A diminution in IgM can be considered of diagnostic significance although the mechanism for this reduction is not known. It has been felt to involve a feed-back mechanism, where one immunoglobulin elevation results in a subsequent diminution in the other immunoglobulins.

THERE HAVE BEEN numerous reports evaluating drug therapy, clinical status and prognosis of patients with multiple myeloma.[1-14] Various criteria have been chosen to judge the effectiveness of therapy, such as subjective wellbeing, relief of bone pain, weight gain, improvement of anemia, recalcification of bone lesions, return toward normal of bone marrow, as well as changes in the immunoglobulin fractions in the serum and the

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From the Immunological Research Laboratory, Mount Zion Hospital and Medical Center, San Francisco.

Grant No. USPHS FR-05472.

Submitted, revised, 24 September 1968.

Supported in part by the Leukemia Project of the Women's Auxiliary, Mount Zion Hospital.

Reprint requests to: Mount Zion Hospital and Medical Center, 1600 Divisadero Street, San Francisco 94115 (Dr. Basch).

urine following chemotherapy.[15-17] A predominant diagnostic criterion for multiple myeloma is the increase of one immunoglobulin fraction in the serum or the appearance of globulin fractions in the urine. Whereas normal serum globulins consist of kappa or lambda light chains bound to the heavy chain of any one globulin (IgA, IgD, IgG and IgM), the paraproteins of multiple myeloma produced by the malignant plasma cells are synthesized with only one light chain type, either kappa or lambda. The same applies for the urinary myeloma globulins.[18] The disappearance or normalization of the paraproteins in both serum and urine can be easily demonstrated and serves as a reliable guide to judge the therapeutic response of a patient.

The purpose of this report is to appraise the effectiveness of therapy in 23 patients with multiple myeloma who were treated with L-phenyl-alanine mustard (melphalan), cyclophosphamide (Cytoxan®), x-ray or steroids or both over a four-year period.

Materials and Methods

Patients were studied at the Mount Zion Hospital and Medical Center and the Harkness Community Hospital and Medical Center in San Francisco between 1963 and 1968. All patients had routine laboratory examinations, including blood cell count, reticulocyte count, platelet count, erythrocyte sedimentation rate, urinalysis, and qualitative test for Bence-Jones proteinuria. Specimens of sternal and iliac crest bone marrow were graded for percentage, morphologic features and maturity of plasma cells. Serum protein electrophoresis was performed on cellulose acetate. Immunoelectrophoresis was carried out by a modification of the method of Scheidegger[19] applying horse IEP-antiserum (immunoelectrophoresis antiserum against whole serum). Precipitation arcs were qualitatively evaluated against a normal control serum.

Response to treatment was demonstrated by serial electrophoresis with the thin agarose gel method introduced by Elevitch.[20] Serum was obtained from blood which was allowed to clot in a 37°C water bath. Urine specimens for electrophoresis were collected for 24 hours, total protein content was determined and an aliquot of 200 ml was dialized and lyophilized for further studies. Typing of light chains and Bence-Jones proteins in serum and urine was performed by immunoelectrophoresis with horse anti-kappa and anti-lambda antiserum, and on Ouchterlony diffusion plates, employing rabbit anti-kappa and anti-lambda antihuman serum.* Quantitative immunoglobulin studies were done by radial diffusion technique,[21-23] employing the Hyland immuno-diffusion plates and standards. Supporting laboratory findings, included blood urea nitrogen, uric acid, calcium, phosphorus and alkaline phosphatase determinations in the serum. X-ray skeletal survey was performed, including chest, skull, vertebrae and pelvis as well as areas of bone pain.

Criteria for Diagnosis of Multiple Myeloma†

The diagnosis of multiple myeloma was established by at least two positive findings of the following criteria (see Table 1):

(1) The presence of greater than 10 percent abnormal plasma cells in the bone marrow, or sheets of plasma cells in a biopsy specimen from a solitary lesion.

(2) Radiographic evidence of osteolytic lesions not due to another malignant process or generalized osteoporosis.

(3) Serum electrophoresis showing a monoclonal spike (myeloma globulin or M-globulin) in the gamma region of either kappa or lambda type, with corresponding high values of one immunoglobulin fraction and diminution in the other immunoglobulin fractions. The monoclonal spike had to show at least 20 percent increase over normal maximal value of the immunoglobulin fraction concerned. Normal immunoglobulin values per 100 ml for adults (according to Hyland radial diffusion plate test instructions) IgA = gamma A = 140 to 260 mg, IgG = gamma G = 700 to 1,500 mg, IgM = gamma M = 70 to 130 mg. The presence of Bence-Jones protein in the serum of either kappa or lambda type.

(4) The presence of Bence-Jones protein in the urine demonstrated by either chemical tests or immunoelectrophoresis.

Additional diagnostic supporting factors:

History: Frequent infections (pneumonitis, pyelonephritis and the like).

Blood chemistry: Hypercalcemia, hyperuricemia, uremia.

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*Provided by Dr. H. H. Fudenberg, U.C. School of Medicine, San Francisco.

†Analogous to: Protocol Committee of the Chronic Leukemia-Myeloma Task Force of the National Cancer Institute (Nov. 1965) (guides for Protocol Studies of Plasma Cell Myeloma).

TABLE 1.—*Diagnostic Findings in 23 Cases of Multiple Myeloma*

			MYELOMA TYPE					*SUPPORTIVE FINDINGS AT DIAGNOSIS*				
Case	*Age, Sex*		*IgA*	*IgG*	*Renal Involvement*	*L-Chain*	*Skeletal X-Ray*	*Hbg*	*BUN (per 100 ml)*	*Calcium*	*Bone Marrow*	*Symptoms*†
1*	75	F	√		0	Lambda	Normal	10.6 gm	11.0 mg	7.3 mg	Abnormal plasmablasts Plasmocytosis	P, W
2	63	F		BJ-P √	+	Kappa	Multiple lytic lesions	9.0 gm	50.0 mg	14.1 mg	8% Plasma cells, atypical immature	P, WL, I
3*	56	M		BJ-P √	0	Kappa	Path. Fracture T_7	8.4 gm	9.0 mg	8.2 mg	Sheets of immature plasma cells	W, WL, P
4	55	M	√	√	0	Kappa	Lytic lesion left ileum	15.2 gm	7.5 mg	10.2 mg	Biopsy of lytic area: plasmocytosis	P, WL
5*	70	M	√		0	Not determ.	Generalized osteoporosis lytic lesion left hip	7.2 gm	16.0 mg	11.7 mg	90% (Sheets) atyp. plasma cells	WL, P, I
6*	56	F	√		0	Not determ.	Lytic lesions Ribs L_4	10.9 gm	20.0 mg	9.7 mg	Infiltrations with immature plasma cells	W, P
7	76	F	√		0	Kappa	Moderate generalized osteoporosis	9.7 gm	12.4 mg	8.6 mg	30% Plasma cells	WL, W
8	55	M		√	0	Lambda	Normal	11.7 gm	18.0 mg	9.4 mg	Approx. 10% abnormal plasma cells	I, W
9*	74	M		√	0	Lambda	Generalized osteoporosis	9.9 gm	15.0 mg	9.7 mg	10% Plasmocytosis	W
10	49	F		BJ-P √	+	Kappa	Path. fracture pelvis	10.6 gm	49.0 mg	13.3 mg	90% Immature plasma cells	W, P
11*	63	M	√		+	Lambda	Normal	8.7 gm	106.0 mg	9.3 mg	Sheets (90%) of plasma cells	I, WL, W
12	55	M		BJ-P √	0	Lambda	Lytic solitary lesion left shoulder	12.8 gm	19.0 mg	12.4 mg	Biopsy of lesion: sheets atyp. plasmacytes	P
13*	69	F	√		0	Not determ.	Lytic lesions skull, general demineralization	12.0 gm	15.0 mg	8.7 mg	10% Plasma cells	W, WL, P
14	56	M		√	+	Kappa	Lytic lesions spine left ramus pubis; General demineralization	8.0 gm	55.5 mg	13.5 mg	90% Atypical plasma cells	P, W, I
15	66	M			+	Kappa	Mult. lytic lesions skull, demineral. spine	9.3 gm	20.0 mg	9.5 mg	Marrow replacement with atypical plasmacytes	P
16	51	F		BJ-P √	+	Kappa	Multiple osteolytic lesions	9.5 gm	22.0 mg	12.0 mg	90% Replacement	P, I
17*	73	M		√	0	Kappa	Generalized demineralization Collapsed T_8	8.1 gm	20.0 mg	9.4 mg	Sheets of immature plasma cells	P, W
18	58	M		√	0	Lambda	Normal	9.9 gm	19.0 mg	9.2 mg	10% Immature plasma cells	W
19*	80	F		√	0	Kappa	Advanced vertebral osteoporosis	9.1 gm	18.0 mg	8.2 mg	Replacement of marrow with atyp. plasmacytes	P
20	44	M	√		0	Lambda	Multiple lytic lesions skull, ribs, spine	8.0 gm	13.0 mg	11.7 mg	Replacement of marrow with atyp. plasmacytes	P, WL, W
21	78	M		√	0	Lambda	Normal	7.8 gm	24.0 mg	8.8 mg	90% Replacement with plasma cells	WL, W
22	72	M		√	0	Kappa	Path. fracture of clavicle	9.3 gm	23.0 mg	10.0 mg	80% Atypical plasma cells	W, WL, P
23	69	F			+	Lambda	Lytic lesion skull, general. osteoporosis	11.2 gm	12.7 mg	9.4 mg	Plasmocytosis	WL

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*Died.

†Symptoms: P = Bone pain; WL = Weight loss; W = Weakness; I = Infection.

√ = Spike.

Physical findings: Palpable tumors, rib tenderness, spine tenderness, evidence of renal failure without hypertension.

Hematological findings: Anemia, leukopenia, thrombocytopenia, accelerated sedimentation rate.

Symptoms: Bone pain, weight loss, excessive fatigue and weakness. In our series, the most frequent symptoms at the time of diagnosis were localized or generalized skeletal pain either alone or in combination with weakness and weight loss (16 of 23 cases, or 70 percent). Recurrent infections were the main complaint in six of 23 cases, and unexplained weakness led to a diagnostic work-up in two patients.

Initial hemoglobin determinations ranged between 7 and 11 gm per liter; three of 23 patients had hemoglobin above 12 gm. Abnormally high blood urea nitrogen (BUN) values were found in four patients, all of whom had pronounced Bence-Jones proteinuria. Three other patients with Bence-Jones proteinuria had BUN values within normal limits.

Serum calcium determinations were decidedly elevated in seven patients, all of whom had radiologic evidence of lytic bone lesions. Lytic lesions were also observed without elevation of the serum calcium, and generalized osteoporosis was not associated with increased calcium values in our series. Four of seven patients with renal involvement had high serum calcium when first seen.

Treatment Program

Melphalan: Up to 70 micrograms per kg of bodyweight per day was given initially, according to tolerance, for approximately two to four weeks. The daily dose was then reduced to a maintenance of 1 to 4 mg per day and regulated by leukocyte counts (required to be greater than 3,000 per cubic millimeter) and platelet counts (required to be greater than 50,000 per cubic millimeter).

Cytoxan®: Cytoxan was usually the second chemotherapeutic agent used in the treatment plan. In four cases it was used first. Following an initial loading dose, maintenance was regulated between 50 and 100 mg per day with the leukocyte count being kept in excess of 3,000 cells per cu mm.

Prednisone: Corticosteroids were prescribed in a dosage starting between 40 and 100 mg daily, and later reduced to 5 to 30 mg per day. Treatment was mainly intermittent, depending on symptoms, anemia and leukopenia, although for patients treated after 1966 it was used more liberally.

TABLE 2.—*Schedule of Therapy in 23 Cases of Multiple Myeloma*

	Chemotherapy†			*X-Ray Therapy‡*	
	Drug and Length of Use (Months)				
Case	*Initial Drug*	*Successive Drugs*	*Months of Drug Therapy*	*No. of Courses*	*Total Exposure*
1	P/ 7	M/ 2	8	—	—
2	C, P/41	—	41	1	1,200
3	C/27	M, A/13	40	3	5.200
4	M/30	—	30	1*	2,000
5	M/10	P/ 9	12	2	4,000
6	M, A/ 2	—	2	4*	5,600
7	M/12	—	12	—	—
8	M/ 6 A/13	C/ 8 P/ 6	19	1	3,200
9	M/17	A/13	17	—	—
10	M/ 4 P, A/25	—	25	7	15,200
11	M/17	—	17	—	—
12	M/26	A/14	26	1*	4,500
13	M, P, A/ 6	—	—	1	2,400
14	M, P/12	A/ 8	12	—	—
15	M, P/12	—	12	1	2,000
16	M/ 8 A/13	—	16	3	7,100
17	C/23	M/18	42	4	9,100
18	M, A/11	C, P/ 4	15	—	—
19	C/ 3	—	3	1	1,600
20	C/18	A, P, M/ 3	21	1	2,000
21	M, A/ 3	—	3	—	—
22	M/ 2	P, A/ 1	2	1	2,000
23	M/ 4	P, A/ 2	4	—	—

* X-ray = initially only ℞.

† Chemotherapy: C = Cytoxan®; M = Melphalan; P = Prednisone; A = Androgens.

‡ Total exposure measured in surface "R."

Androgens: Fluoxymesterone (Halotestin®) was administered in daily doses of 10 to 20 mg per day to all patients.

Supporting Therapy: Blood transfusions as needed.

X-Ray Therapy: When localized bone pain was the most prominent symptom, a course of radiation therapy was given, consisting usually of three to five sessions of approximately 400 to 500 r each. Additional courses were given when localized pain recurred. (See Table 2.)

All patients included in this report had chemotherapy for at least two months. Three additional patients in whom multiple myeloma was diagnosed during the period of this study were not included in this series because one was not treated with chemotherapy, one died of a myocardial infarct after one month of therapy, and one moved out of town and follow-up serum specimens could not be obtained.

TABLE 3.—*Results of Treatment in 23 Cases of Multiple Myeloma*

		Maximal or Initial Values of Immunoglobulins (mg per 100 ml)			*Values in remission or refractory values (mg per 100 ml)*			
Case	*Time Observed (months)*	*IgA*	*IgG*	*IgM*	*IgA*	*IgG*	*IgM*	*Evaluation of changes of Para-protein level in serum and/or urine*
1	31	*1050*	350	25	*1650*	120	23	NR
2	41	180	580	16	145	830	17	Disappearance of BJ proteinuria R
3	40	25	*3000*	14	60	*1200*	22	R
4	31	*800*	*1800*	55	*225*	*1250*	54	R
5	132	*710*	520	12	*260*	820	none detectable	R
6	36	*900*	840	32	*760*	920	22	Essentially unchanged
7	30	*580*	1225	22	*490*	1350	22	Essentially unchanged
8	22	26	*5200*	13.5	20	*2300*	none detectable	R
9	18	135	*2300*	36	65	*1550*	34	R
10	28	51	1000	29	160	1500	78	Disappearance of BJ proteinuria R
11	17	*580*	700	14.5	*930*	620	trace	NR
12	29	200	2650	105	230	*1450*	70	R
13	6	*1175*	375	22.5	*580*	375	17	R
14	11	250	670	17	85	870	25	Disappearance of BJ proteinuria R
15	11	32	650	11.5	30	1100	14	Marked decrease of proteinuria R
16	16	45	1000	14	34	550	none detectable	Disappearance of BJ proteinuria R
17	45	22	*3500*	16	25	*4000*	20	NR
18	14	25	3200 to *5200*	16	19	*2000*	23	R
19	23	38	*5500*	none detectable	. .	*2700*	. .	R
20	41	*1320*	550	11	*1000*	870	trace	R
21	4	19	*2200*	16	18	*1800*	trace	Essentially unchanged
22	3	38	*2650*	22	17	*3100*	11.5	NR
23	4	37	880	25	46	430	16.5	Marked decrease of proteinuria R

Normal Values (mg per 100 ml): A, 140-260; G, 700-1500; M, 70-130 (Hyland).
Legend: Italics indicate myeloma-globulin; R = responding; NR = not responding.

Criteria of Response:

Serum: Normalization of myeloma globulin (M-globulin) fraction or decrease of M-globulin fraction of 50 percent of the maximal value before treatment.

Urine: Pronounced decrease of total protein in 24-hour collection of urine on two successive determinations, or immunoelectrophoretic disappearance of Bence-Jones protein in the urine.

Anemia: Maintenance of more than 10 gm of hemoglobulin over a period of more than three months without transfusions, or rise of more than 2 grams in hemoglobin.

Calcium: Reduction to less than 11 mg per 100 ml when initially elevated.

BUN: Return to less than 25 mg per 100 ml when previously elevated.

Performance Status: Increase of activity of 2 points with associated reduction of pain, for at least two months. (Activity is graded according to the Eastern Group Scale*: 0 = asymptomatic; 1 = with symptoms, but ambulatory; 2 = in bed less than half a day; 3 = in bed more than half a day; 4 = totally bedridden).

We are not including bone marrow follow-up studies as a criterion of response, as these findings vary considerably with the site of aspiration. We also noted that the bone marrow may essentially remain unchanged in periods of remission when all other criteria show good response to treatment.

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*Scale derived from Cancer Chemotherapy Reports, Vol. 57, No. 1-7, Dec. 1967, p. 518.

Results

The results of treatment in the 23 cases studied were divided into three categories (Table 3):

(1) *Patients responding to treatment with an improved disease status.* The leading criterion for improvement in this group is the normalization of the myeloma-globulin (M-globulin) fraction or a decrease of this fraction to 50 percent of pretreatment levels. Disappearance of Bence-Jones proteinuria or pronounced decrease of total protein excretion in the urine was also considered satisfactory response to treatment. Simultaneously this group was judged by an improved performance status, as well as hematological and blood chemistry findings as outlined. In our series 16 of 23 cases fall into this category (Cases 2, 3, 4, 5, 8, 9, 10, 12, 13, 14, 15, 16, 18, 19, 20, 23). Thus 70 percent of patients responded with a definite improvement to therapy in their clinical status concurrent with normalization of their M-globulin.

(2) *Patients not responding to treatment, the disease progressing.* These patients showed a gradual increase in M-globulin associated with progressive deterioration in their clinical status, three of the four patients in this category dying (Cases 1, 11, 17, 22).

(3) *Patients with essentially unchanged disease status.* There were three patients in this category (Cases 6, 7, 21). They received chemotherapy over a relatively short time (two to three months) and showed either poor clinical response or minimal decrease in M-globulins.

Myeloma patients show abnormally high amounts in two major fractions of gamma-globulins, namely IgA and IgG. This increase is immunoelectrophoretically documented either as one heavy arc or as a split or notched arc. An analysis of the 23 cases in this report revealed seven cases (30.4 percent) to be of the gamma-A paraprotein type and 13 cases (56 percent) of the gamma-G paraprotein type, which concurs with reports of other investigators, who found 30 percent gamma-A and 60 percent gamma-G monoclonal spikes in their series of myeloma patients. Two of our 23 patients (Cases 15 and 23) did not have myeloma globulins in their serum. Both had severe kidney involvement with Bence-Jones proteinuria. The thermal characteristics of Bence-Jones protein in the urine as shown by the heat test are found in from 13 percent to 80 percent of myeloma cases, depending upon the techniques employed,[24] although 90 percent of patients with the disease have Bence-Jones protein in the concentrated urine by immunoelectrophoresis. In Case 4 (Table 1) there was a combination of gamma-A and gamma-G paraprotein in the serum. The patient did not show signs of disseminated disease, but radiologically well defined lytic lesions were seen in the hip and in the seventh cervical vertebra. Biopsy of the hip-lesion showed plasmacytoma.

Light chains have been analyzed by various investigators, who report that 60 percent of the light chains are of the kappa type and 40 percent are of the lambda type.[7] Williams and Chase,[18] in typing of light chains by immunoelectrophoresis and Ouchterlony methods, noted that 11 of 20 patients were kappa type and nine of 20 were lambda type. The light chain type of three patients could not be determined due to insufficient amounts of serum. These patients were of the IgA type.

In our series we saw a precipitous drop or return to normal values in myeloma protein in 10 of 23 cases. These patients simultaneously had an increase in hemoglobin and improvement in performance status. In six of seven cases with severe kidney involvement, but essentially normal values of gamma globulin in the serum, response was documented by disappearance of Bence-Jones proteinuria, reduction of albuminuria, reduction of BUN and increase in creatinine clearance. Six of the seven patients with renal disease were living when the study was terminated. One patient (Case 11) initially improved with an increase in creatinine clearance and renal function and diminution in serum creatinine and BUN, although pronounced anemia and proteinuria persisted. He died as a result of a transfusion reaction with renal failure. (This case is simultaneously listed as gamma-A myeloma). Nine of 23 patients in the series had died at the time the study ended. Of the nine, five showed IgA myeloma protein (Cases 1, 5, 6, 11, 13) and four showed IgG myeloma protein (Cases 3, 9, 17, 19). The mean survival time of patients with decreases was 25.5 months, with a range of 6 to 132 months. Two of the nine patients died of generalized progressive myeloma and the other seven of various non-related disease. The mean observation time of all patients in our group was 27.4 months, and the range was from three months to eleven years.

A study of patients with gamma-G paraproteins receiving alkylating therapy or combined alkylating and prednisone therapy revealed a gradual reduction in abnormal proteins during approximately 12 months of therapy. Reduction when once obtained was found to be generally maintained. Analysis of the reduction in gamma-A-paraproteins on alkylating therapy plus Prednisone reveals a more rapid fall, with a nadir being achieved in approximately ten months. The patients responding in this series had a shorter mean life span than that reported by other investigators.[5,7,25] This is probably due to the small number of cases in the present study.

Twenty-two of 23 patients had a concomitant decided reduction in IgM, and in only two cases did it return to normal during therapy. The exception was Case 12 (Table 3), a case of a solitary plasmacytoma without disseminated disease, in which normal IgM values were maintained throughout. In Case 4, also one of solitary plasmacytoma without dissemination, IgM values returned to low normal under chemotherapy. Case 10 was an exception in which the IgM remained subnormal until prednisone therapy was begun, and then rose into the normal range.

In Cases 4 and 12, biopsy specimens were taken from solitary lytic lesions to confirm the diagnosis of myeloma. Serum analysis in Case 4 revealed a biclonal spike consisting of IgG and IgA while in Case 12 there was a monoclonal spike of IgG. In Case 5, the patient was first observed in 1954 with a solitary myeloma which was initially well controlled with two courses of radiation therapy. On relapse later, the disease progressed into generalized myeloma some ten years after onset of the original lesion.

Cohen, Svien and Dahlin[26] and Griffith[27] reviewed a large series of myelomatous bone lesions. They reported that dissemination of the disease into generalized myeloma occurred between two and a half and eight years after initial diagnosis. One of Cohen's patients lived more than 21 years before signs of dissemination appeared. These findings concur with Engle's[28] statement that in patients with solitary plasmacytoma a condition indistinguishable from generalized myeloma will ultimately develop. Thus, in cases such as Cases 4 and 12 in our series, the prognosis is guarded even though the patients are in satisfactory remission at the present time.

Discussion

Since MacIntyre and Watson in 1847 first described a condition of "osseitis mollitus" with urinary secretion of an unknown protein fraction, many investigators have described changes of the gamma globulins in multiple myeloma.[29-33] The first physician to relate the entity of multiple myeloma to an over-production of plasma cells was Dr. James H. Wright in 1900.

Multiple myeloma is a malignant tumor of plasma cells, primarily involving the skeleton but also occurring in soft tissues. The malignant plasma cell produces abnormal proteins which are reflected by changes in the immunoglobulin fractions in serum or urine or both. Two distinct patterns of hypergammaglobulinemia are recognized: (1) The diffuse increase of all globulin fractions, IgA, IgD, IgG, and IgM (polyclonal gammopathies) which occurs in response to antigenic stimulation, as in neoplastic, inflammatory and collagen diseases. Usually IgG is most prominent; and (2) the monoclonal type with homogenous increase in one M-globulin fraction.

Monoclonal spikes may be seen in benign[34-37] as well as in malignant processes and represent a significant finding in multiple myeloma.[15,16,25,27]

Only a few cases have been reported where a myelomatous process was consistent with an increase in two distinct fractions of immunoglobulins.[38,39] This biclonal pattern implies production of two types of plasma cell clones, but it is possible that the origin of both immunoglobulins derives from a single cell line. In Case 4 in the present series a biclonal spike of both A-myeloma protein (AMP) and G-myeloma protein (GMP) was demonstrated. Both sternal and iliac crest bone marrows were negative for myeloma over a 30-month period in this patient. X-ray studies revealed osteolytic lesions in the right hip and subsequently in the seventh cervical vertebra.

We concur with Caggiano and coworkers,[6] Costa and coworkers[40] and Salmon and his associates[5] that combined administration of melphalan and prednisone induces a higher remission rate with more general improvement than melphalan alone. Poor risk myeloma patients tolerate chemotherapy in increased doses when prednisone is used. They respond with better appetite, clinical wellbeing, stabilization of leukocyte count and diminution of generalized toxic effects. In one case in our series (Case 20) a patient with previous chemotherapy of three years' duration was seen in relapse with severe pain, performance status 4, pronounced leukopenia and extensive myelomatous involve-

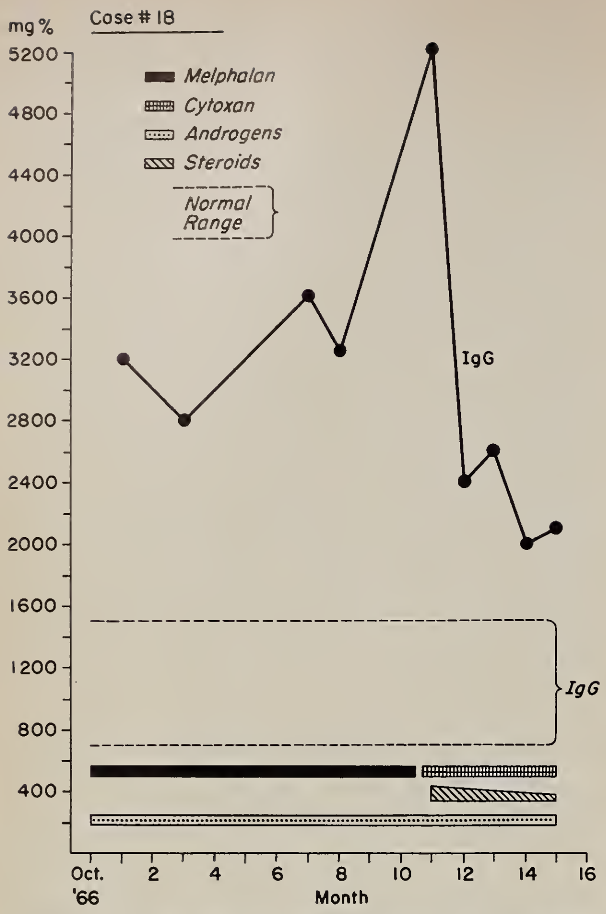

Chart 1. — Response to prednesone and Cytoxan® in combination after responsiveness to mephalan had abated.

ment with almost total marrow replacement. He responded dramatically with a good clinical remission (performance status 1) within a four-week period, although the bone marrow two months later remained essentially unchanged.

The patient in Case 18 was unresponsive after a year of melphalan therapy. Prednisone then was started in combination with Cytoxan,® which resulted in a precipitous drop in IgG from 5,200 mg to 2,000 mg per 100 ml and a decided increase in hemoglobin and performance status, from status 3 to status 1 in one month of treatment. (See Chart 1.) In three of 23 cases, prednisone was used in high doses after failure to improve or decreased response to previously effective chemotherapy was manifested by increase in M-globulins. There was a concurrent increase in the leukocyte count, allowing the reinstitution and continued use of alkylating agents.

The mechanism of the prednisone action is not fully understood. Since the catabolism of immunoglobulins is increased in myeloma,[41,42] one may speculate that prednisone therapy reduces production of abnormal globulins in the plasma cells. Prednisone was not found to reduce the general myelomatous process or the number of malignant plasma cells in follow-up studies of bone marrow in our patients. The notable improvement in hemoglobin is probably secondary to a decrease in hemolysis as well as an increase in erythropoiesis. An unpublished communication of Dr. H. H. Fudenberg states that there may be acceleration of the disease process and earlier death in multiple myeloma patients with predominant renal involvement when they are treated with prednisone.[43] We do not have sufficient data to support this finding.

Snapper[31] reported that Bence-Jones protein in the urine is found more frequently in myeloma patients where serum immunoglobulins are within normal range (see our Cases 15 and 23). Typing of the Bence-Jones protein revealed that the light chain type of the urine and the serum were identical, either kappa or lambda. This reflects a similar origin for both Bence-Jones protein and serum M-proteins, namely the neoplastic plasma cell.

Seven of the 23 patients had severe renal involvement with uremia and pronounced proteinuria. Three of these seven patients were originally treated for chronic renal disease for many months before myeloma was diagnosed. Five of seven patients with renal involvement, however, showed a monoclonal or Bence-Jones protein in the serum at some stage of their disease. In these cases the myeloma serum globulin was reduced during periods of remission and increased when relapse occurred.

Wochner[44] recently showed that patients with uremia have an alteration in the endogenous catabolism of Bence-Jones protein by the renal tubule. In uremia, as the kidney is unable to catabolize the excess Bence-Jones protein made by plasma cells, some of it is retained in the serum. The total serum M-globulin is thus increased. With improvement in the renal tubular function, the serum M-globulin decreases.

Summarizing the results of treatment in the 23 cases in our series: Chemotherapy was initiated with Cytoxan® in five cases and melphalan in 17 cases. It is our feeling that these alkylating agents are equally effective in treatment of myeloma, with both clinical response and reduction of immune globulins demonstrated in the majority of cases.

In three of 23 cases, a course of radiotherapy was given before any alkylating agent was started, without producing changes in the myeloma protein values. Melphalan therapy then was begun, with reduction of myeloma proteins in two of the three cases. Radiation therapy was used initially or in combination with chemotherapy in 15 of 23 cases. When localized bone pain was the presenting or subsequent complaint, irradiation produced dramatic relief of pain. Patients received between one and seven courses of x-ray therapy with the total doses varying between 1,200 and 15,000 roentgens.

Eight of 23 patients received chemotherapy alone, with relief of bone pain and increase of hemoglobin and performance status. From our experience we believe that, as supporting therapy, androgens enable patients to tolerate a higher dose of chemotherapy, which concurs with the findings of Brodsky.[45,46] In our series 21 of 23 patients benefited substantially from administration of Halotestin®: hemoglobin and white blood cell count increased and the patients appeared to require fewer transfusions.

Nine of 23 patients had died at the time of this report. Seven of nine deaths were related to infections—pneumonia in four cases and septicemia in three. Herpes zoster occurred in three cases in our series. The causes of infections were multiple: leukopenia due to marrow replacement by myelomatous infiltrations; drug therapy with secondary leukopenia; and incompetent immunological status with pronounced decrease in functioning gamma globulin. Gamma globulin has been used as adjuvant therapy in treatment of infections. A recent review by Salmon and coworkers[41] has shown that there is decided catabolism of gamma globulin and that the currently used method of administration as well as the quantity of gamma globulin administered, is insufficient to combat infectious process found in myeloma patients.

The increasing supplanting of normal bone marrow elements by malignant plasma cells may cause thrombocytopenia, and bleeding episodes or purpura are frequently encountered. Three of the 23 patients in the present series (Cases 3, 6 and 21) had bleeding from the gastrointestinal or the urogenital tract. One patient (Case 1) had Henoch-Schoenlein-like purpura when first observed.

Generic and Trade Names of Drugs

Cyclophosphamide	*Cytoxan®*
Fluoxymesterone	*Halotestin®*

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LINCOMYCIN IN PEDIATRIC OTITIS MEDIA

"What do you do for a child with otitis media who has a history of allergy to penicillin, sulfonamide, and erythromycin and is under age six so you don't want to use tetracycline? You have another drug to turn to—lincomycin. Lincomycin is quite effective against the streptococcus in the test tube and may be effective clinically although we need more information. It's rather effective against the staphylococcus and really rather good against the pneumococcus. It's not very good against the *Haemophilus influenzae*; and unfortunately, as you remember, that's one of the more common causes of otitis media. But I would consider seriously trying lincomycin in a case like that and would get a nose culture. The correlation between nose cultures and middle ear cultures is not good. It's better [however, than the correlation with] throat cultures; so if I had only one, I'd get a nose culture or perhaps a combined nose and throat culture to see whether I could find out what was going on in the middle ear. If it cultured *Haemophilus influenzae*, I'd be less confident the lincomycin was going to work. On the other hand, if you had a beta hemolytic streptococcus or a pneumococcus, I'd have reasonable confidence that lincomycin would work."

—BENJAMIN M. KAGAN, M.D., Los Angeles

Extracted from *Audio-Digest Pediatrics*, Vol. 14, No. 9, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

■ *A cooperative phenylketonuria screening program involving private nongovernmental laboratories, individual physicians and local and state health departments has been in operation for two years. The system has evolved to the point where practically all newborns are tested. The accuracy of laboratory work has been verified by an ongoing evaluation program which has resulted in continual improvement in level of performance. There are two areas in which some beneficial changes might be considered. One is the reduction of costs of the testing and follow-up by increasing volume and centralization of work. The other is greater cooperation of the medical community in collecting the data necessary to evaluate the program and expedite the final diagnosis.*

Two Years of PKU Testing in California

The Role of the Laboratory

GEORGE C. CUNNINGHAM, M.D., *Berkeley*

THE SCREENING OF NEWBORN INFANTS for phenylketonuria has become a standard procedure and in many cases is required by law. An important aspect of the effectiveness of such a program is the ability of the screening laboratory to perform the test reliably and expedite follow-up of suspicious results. This report will review the PKU program in California with emphasis on the role of the testing laboratory.

The recommendations of many authorities, including the American Academy of Pediatrics[1] and the U.S. Children's Bureau,[2] indicated that such screening should be performed in central laboratories. It was believed that such laboratories could more easily monitor their precision and accuracy. The volume of testing would reduce the cost of testing and a central reference point for information would allow for immediate and direct follow-up of positive screening results.

From the Hereditary Defects Unit, California State Department of Public Health, Berkeley.

Supported in part by a grant from the United States Children's Bureau.

Submitted 2 April 1968.

Reprint requests to: Hereditary Defects Unit, California State Department of Public Health, 2151 Berkeley Way, Berkeley 94704.

In California, the screening program has been implemented in a unique way. Rather than attempting a centralization of testing, the resources of hospital and private laboratories have been used. Any licensed clinical laboratory may apply to the State Department of Public Health for approval to participate as a screening laboratory. On the basis of available information, the Department has approved the microbiological inhibition assay (MIA)[3] and the fluorometric method[4] as the only techniques applicable to newborn screening. Laboratories report results of all positive and follow-up tests to the Department as a part of a comprehensive reporting system. The laboratories establish their own fee for the test, which is paid by the parents. This report summarizes the first two years' experience with regard to participation of the hospital, the laboratory and the physician.

Results of Program

At the end of the second year of the program, 39 cases of PKU had been detected and diagnosed as a result of screening 624,998 newborns. This is an incidence of one case per 16,000 infants tested. In 1966, 307,704 infants were tested and 16 cases detected. In 1967, 317,294 infants were tested and an additional 23 cases discovered.

This incidence is below that predicted from screening programs conducted in other states and foreign countries (1 in 10,000). It is not clear from the statistics relating to the other studies whether the higher incidence reported represented cases of high serum phenylalanine or true phenylketonuria. All diagnosed cases are carefully analyzed to exclude other causes of high serum phenylalanine. The incidence also reflects random occurrence of cases from birth cohort to birth cohort.

Hospital Participation

Information was requested from 436 hospitals and at completion of our tally all had supplied the requested information.

During the period from 1 January 1966 to 31 December 1966, the hospitals reported 312,032 live infants discharged, of which 307,704 had had the test, approximately 98.6 percent of the total reported. From 1 January 1967 to 31 December 1967, the hospitals reported 320,805 live infants discharged, of which 317,294 had had the test, approximately 98.9 percent of the total reported. There are no definitive statistics available on the number of live births in 1966, but the Bureau of Vital Statistics estimates there were 315,265 births in these hospitals. This represents reporting of 99 percent of the births.

The State Department of Public Health is taking appropriate action to keep the number of infants not tested to a minimum. The reasons infants were not tested are summarized in Table 1.

The law allows exception in the case of parental objection and medical contraindication to testing. Most of the infants listed in the table as "transfered to another hospital" were subsequently tested. Infants in categories 4, 5, 6 and 7 in Table 1—that is, those with inadequate specimens or with the test omitted in error before discharge from the hospital—have been referred to the local health departments and many of them may have received the test after discharge. While there is some degree of under-reporting of births and a few infants are not being tested, it is apparent that the program has been highly successful in insuring that the vast majority of infants receive the test.

Laboratory Participation

The laboratory is responsible for obtaining a reliable initial test and communicating this information to the physician and the Department. The California regulations provide that the physician be notified immediately by telephone and that he arrange for a repeat test within seven days. Assistance in this regard is available from the local health departments.

In 1966 the laboratories performed 311,953 initial tests, 1,162 of which (0.37 percent) were

TABLE 1.—*Distribution of Infants Not Tested*

	1966		*1967*	
Reason For Not Testing	*Number*	*Percent*	*Number*	*Percent*
1. Parental objection on religious grounds....	252	(5.8%)	202	(5.8%)
2. Medical contraindication to testing........	91	(2.1%)	197	(5.6%)
3. Transferred to another hospital for testing..	773	(17.9%)	977	(27.8%)
4. Inadequate specimen obtained in hospital...	200	(4.6%)	187	(5.3%)
5. Omission of test by error or no reason given	2528	(58.4%)	774	(22.1%)
6. Discharged "too early" for reliable test.....	283	(6.5%)	81	(2.3%)
7. Miscellaneous	201	(4.6%)	1093	(31.1%)
Total Infants Not Tested................	4328	(100.0%)	3511	(100.0%)

positive. According to reports received from the laboratories, a repeat test was obtained on 861, or 74 percent of the infants with initial positive tests; in 134 cases the test was again positive. With the cooperation of local health departments, the Department obtained information on the disposition of these 134. All were determined to be temporary elevations and not phenylketonuric except for the 16 diagnosed PKU and five lost to follow-up because of death or inability to locate.

The large number of initial positive tests which were not repeated (299) is a product of inaccurate reporting by the laboratories and their failure to report repeats of initial positive tests to the local health departments in the first and second quarters. Health departments reported that repeat tests were done in all but 74 of the 905 cases in which initial positive tests were reported to them.

In 1967 the laboratories performed 334,831 initial tests, of which 905 or 0.27 percent were positive. The follow-up figures for this year are more accurate, as every initial positive reported by the laboratories was verified before being included in the count. At the close of the reporting period a repeat test had been obtained on 799 or 87 percent of the 905 initial positives, 117 of which were again positive. Twenty-four had been lost to follow-up and in 82 cases a repeat test was pending. All but one of the 117 infants with doubly positive tests were diagnostically evaluated. Twenty were confirmed as having PKU, eight are still being studied, and the rest were found to be not phenylketonuric. By the time these cases are closed, we anticipate follow-up tests will have been obtained on 90 percent or more. In order to estimate the effectiveness of follow-up, a thorough study of follow-up activity in the third quarter of 1966 was carried out. There were 302 initial positives reported in this period. Of these, 193 were repeat tested in the third quarter and 77 in the fourth quarter. There were 32, approximately 10 percent of the initial positive, that had not had repeat test results reported to the Department six months after the initial positive test. In ten of these instances the cases were closed because the parents moved without forwarding addresses, and one infant died in the interim. Considering the logistic difficulties involved, this study was interpreted as indicating a reasonably complete, if at times undesirably slow, follow-up of initial positives. More data is being collected to document the exact time lag between the first positive result and the follow-up test and results.

It is not possible to answer in a definitive fashion why follow-up of initial positives is sometimes so slow. In some instances the laboratory has not pursued its obligation to inform the physician and Department promptly, but in many cases the physicians are at fault. It requires special effort to arrange for retesting and interpretation of results to the family. Some physicians are not aware of their legal obligations and see no necessity of repeating a test when the positive level is low. Only if the physicians are conscientious and cooperative can the early detection of PKU be assured. It is important in evaluation of this kind of effort to have documented results on all babies with positive tests so that implementation can be made more effective and practical with a minimum of effort for all concerned.

With the cooperation of participating laboratories, the reporting forms have been improved and are currently being converted to a punched card data collection system to simplify monitoring and follow-up reports in this program.

Methods of Laboratory Evaluation

The specimens used to evaluate laboratory performance were prepared in the following manner: Outdated human blood was obtained from the blood bank, thoroughly mixed for homogeneity and divided into a suitable number of portions. One portion was used without further treatment. To the other portions, phenylalanine solution (200 mg per 100 ml) in isotonic saline solution was added in varying amounts to obtain concentrations desired, usually a high normal, approximately 3 mg per 100 ml, a low abnormal in the range 4 to 6 mg per 100 ml, and a high abnormal level, 7 to 10 mg per 100 ml, with respect to the screening level of 4 mg per 100 ml. The exact values used for each evaluation are given in Table 2.

All specimens were prepared, assigned random numbers, and mailed on a Monday to allow for analysis that week. Specimens were to be done on arrival at the laboratory and results returned by the following Monday. This was to minimize the effects of change of concentration with time, and to speed up the process of returning results to participants.

Laboratories approved for the microbiological inhibition assay method received filter paper soaked with whole blood. Laboratories approved for the fluorometric test received liquid whole blood. The unknowns were supplied in limited amounts so that only one or two determinations could be run.

Evaluation Criteria

For the fluorometric test, where a numerical value is available, the best estimate of the true value was taken as the mean of all values reported by the participating laboratories after excluding very extreme values. The latter were defined as values beyond three standard deviations of all reported values around the mean. On a few occasions the distribution of values was such that, even after such correction, the mean was displaced by abnormal collections of values. In these instances the mean of 20 determinations by the Department's laboratory was used. An acceptable range was established by taking three standard deviations as calculated for the day-to-day test variability in the Department's laboratory. Each value reported by a laboratory was then classified as acceptable or unacceptable. Table 2 gives the values used to determine acceptability in each evaluation. Values outside of this range were regarded as unacceptable values.

Three standard deviations, as determined in our laboratory, were used instead of the conventional two standard deviations, since it was felt that until the laboratories had had some experience with the program, and some opportunity to accurately standardize their techniques, it would be unfair to prescribe the customary limits. On the other hand, use of the standard deviation between laboratories would have given an unacceptably high tolerance of error. It is anticipated that the limits of tolerance can now be narrowed as indicated by the results of our surveys.

All laboratories were given five unknowns on the first evaluation (March to May 1966). Laboratories with at least four values in the acceptable range were classified as satisfactory. On the second evaluation (5 December 1966), 13 unknowns were mailed, ten of them being from the same specimen. This gave four levels. In addition, a standard deviation was calculated from the ten identical specimens to give an estimate of precision. Acceptable values on at least four of these five criteria were classified as satisfactory. The July 1967 mailing consisted of six specimens, two from each of three levels.

Acceptable limits for the MIA method were more difficult to establish. Reporting was frequently in terms of ranges—for example, between 2 and 4 mg per 100 ml was reported "less than four." A single numerical value was assigned each report according to the following scheme:

Reading Reported	*Value Assigned (mg per 100 ml)*
0	Repeat
Less than 2	1
Equal to 2	2
Greater than 2 but less than 4	3
Equal to 4	4
Greater than 4 but less than 6	5
Equal to 6	6
Greater than 6 but less than 8	7
Equal to 8	8
Greater than 8 but less than 10	9
Equal to 10	10
Greater than 10 but less than 12	11
Equal to 12	12
Greater than 12 but less than 20	16
Equal to 20	20
Greater than 20	20+

All reported values were used to calculate the mean for the MIA technique. These means were found to correspond well with those obtained in the Department by the fluorometric technique and by laboratories performing fluorometric determinations on the same specimens, although the variations of the MIA results were much larger.

Ranges for satisfactory performance using the MIA technique are also detailed in Table 2. These were selected empirically, as no data were available on the reproducibility, in terms of standard deviation, for the method at the time of these evaluations. The standard deviation obviously increases with increasing concentration, and no valid figure

TABLE 2.—*Means and Acceptable Ranges of Phenylalanine Unknowns (mg per 100 ml)*

Evaluation Date	*MIA* Mean*	*Accepted Range*	*Evaluation Date*	*Fluorometric Mean*	*Accepted Range*
3-28-66	2.0	0- 3.9	4-18-66	1.0	0.7- 1.3
	5.3	4.0- 7.9		4.4	3.5- 5.3
	9.7	6.1-12.0		8.0	6.4- 9.6
4- 4-66	1.2	0- 3.4	4-25-66	1.8	1.5- 2.1
	5.1	4.0- 7.9		6.6	5.6- 7.6
	9.3	6.0-12.0		10.8	9.3-12.3
5- 2-66	1.1	0- 2.0	5-16-66	1.5	1.1- 2.1
	4.5	2.1- 7.9		4.6	3.6- 5.6
	8.7	6.1-12.0		7.2	5.2- 9.2
12- 5-66	1.4	0- 4.0	11-28-66	1.8	0.2- 3.4
	5.6	3.0- 8.0		3.6	2.2- 5.0
				5.2	3.1- 7.2
	10.6	6.0-20.0		9.7	6.6-12.9
6-26-67	1.4	0- 3.0	7-17-67	2.2	1.5- 2.7
	4.7	3.0- 7.0		6.0	4.2- 7.8
	5.6	4.0- 8.0		8.4	6.0-10.8
	8.1	5.0-11.0			

*MIA=microbiological inhibition assay.

could be used to calculate reasonable confidence limits. Laboratory performance is classified as unsatisfactory if unacceptable values are reported for more than one concentration level.

Results of Laboratory Evaluations

The first evaluation of fluorometric technique combined the results of March, April and May 1966. Of the 93 laboratories returning results, 19 (20.4 percent) were unsatisfactory. On the second evaluation (December 1966), of 85 reporting laboratories, 15 (17.7 percent) were unsatisfactory. The most recent evaluation (June 1967) had four (5.9 percent) of the 68 laboratories evaluated in the unsatisfactory category.

With the MIA technique, the figures were: Of 144 laboratories responding, 14 (9.7 percent) were unsatisfactory on the first evaluation. On the second evaluation, eight of the 134 laboratories reporting (6 percent) were unsatisfactory, and the latest results indicate only six (4.8 percent) of the 126 participating laboratories were in this category. These results, which do not include laboratories discontinuing participation or failing to return reports, are summarized in Table 3.

The first point that must be made is that unsatisfactory performance as defined in this report does not imply that overall operation or performance of the laboratory was unsatisfactory. Most laboratories experiencing difficulties were able to correct their procedure and perform acceptably on subsequent testing. Moreover, this was the first year of operation of this program and improvement has been seen with additional experience. Initially, several laboratories with minimal experience or limited demand for the determination requested approval. Many of these have discontinued participation. At the inception of the program (March 1966) there were 245 participating laboratories. This number has progressively decreased and the number of approved laboratories is now 174. The proportion using the fluorometric technique has decreased from approximately 40 percent to 30 percent. At first, roughly two-thirds of approved laboratories were performing fewer than ten tests per quarter. This proportion dropped to 3 percent last year.

TABLE 3.—*Data on Unsatisfactory Performance by Laboratories*

Evaluation Date	*Laboratories Participating*		*Unsatisfactory*	
			Number	*Percent*
March-April-May 1966	Fluor.	93	19	20.4
	MIA	144	14	9.7
	Total	237	33	13.9
November-December 1966	Fluor.	85	15	17.7
	MIA	134	8	6.0
	Total	219	23	10.4
June-July 1967	Fluor.	68	4	5.9
	MIA	126	6	4.8
	Total	194	10	5.3

In comparing results of the fluorometric and MIA methods, it must be borne in mind that the criteria for acceptable performance were broader for the latter group because of the difficulties of setting limits with a semi-quantitative technique. As data is accumulated on the MIA technique, it is anticipated that acceptable limits will be narrowed. While both methods give reasonably accurate results as means, the reproducility of the fluorometric method is superior. Attempts to measure intralaboratory variation yielded a coefficient of 20 percent for the MIA technique and 10 percent for the fluorometric technique. A detailed analysis of each method is now being prepared and standards will be established in the near future.

Efforts are currently under way to improve performance. To avoid excessive variation due to too many minor modifications, the Department has circulated the technical details of the method as performed in our laboratories. We have also developed a standardized method of reading and reporting the MIA test. Increased support of the program would allow the Department to experiment with better methods of sample presentation and with the provision of certified reference standards. The Department will attempt to monitor variability of commercial standards used in the program and study variables in procedure used. Workshops in fluorometric and MIA techniques are being planned, and it is hoped that increased staff will allow on-site visits to laboratories unable to correct problems on their own.

Cost-Benefit Analysis of Program

If the 39 cases detected had gone undetected, eventual care of the patients in state hospitals would have cost $6,318,000 based on an estimated 30-year minimum life expectancy in the institution at a cost of $5,400 per patient per year. In addition these persons will be productive taxpayers and their families will have been spared the tragedy of mental retardation. The tax-supported costs of this program, per case, have amounted to less than $2,500 for screening and $8,000 for ten years' treatment services per patient, the latter provided through Crippled Children Services. The total cost of detection and treatment thus far amounts to less than half a million dollars.

In March of 1966, participating laboratories were requested to indicate their charges for performance of the test. The charge for the microbiological inhibition assay test varies from $0.75 to $6.00. The mean charge was $2.30. For the fluorometric method, the range was $1 to $12 with a mean of $3.03. A repeat survey done in September 1967 reveals that the mean charge for the MIA technique has increased to $2.98 with a range of $0.90 to $7.50, and the mean for the fluorometric test is $4.91 with a range of $0.75 to $15.00. Analysis of these reports indicates that some reduction in costs could be achieved by increased volume of testing. The costs of test performance on the total newborn population of approximately 312,000 amounted to a little less than $900,000 in 1966. This amount was paid by the parents of newborns as part of their overall hospital maternity costs. The salaries of personnel administering this program in the state and local health departments, and operating expenses, the cost of forms and the like have been estimated at approximately $90,000 the first year and $60,000 in 1967. The administrative costs were necessarily higher the first year than would be expected once the program was well established. These costs were funded by federal, state and local taxes.

These costs might be compared with those reported from some other states that use centralized testing. Massachusetts reported a cost of $50,000 to test 114,000 infants; New York, for 500,000 tests, requested $227,343 for laboratory support. The District of Columbia requested $35,545 to screen 15,000 births. New Jersey appropriated $10,000 in 1965 for 60,000 births, and Wisconsin $27,000 for 56,000. Rhode Island reported a cost of $1.14 per test in the first year of its program. The cost of administration is apparently not included in these figures. Illinois, with 200,000 births, appropriated $400,000 to pay for a non-centralized program similar in many respects to the one in California.

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THE "AMPICILLIN RASH" QUANDARY

How can you identify a rash caused by ampicillin?

"The rash that you get from ampicillin is very much like the rash you get with a viral disease, and this is one of the disturbing things. You treat a child with a respiratory disease; you give him a drug like ampicillin; and within a few days, he may be better but he now has a rash. Is it due to the respiratory disease, due to a viral disease, or due to ampicillin? This is one of the reasons I don't like to use ampicillin in respiratory disease; once you have that rash, you can't tell whether it's due to the disease or due to the ampicillin. Ampicillin is such a valuable drug that it would be much better to use something else. Save it until when you really need it."

—BENJAMIN M. KAGAN, M.D., Los Angeles

Extracted from *Audio-Digest Pediatrics*, Vol. 14, No. 9, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

Current Therapy of Rheumatoid Arthritis

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■ *The well informed and well motivated patient with rheumatoid arthritis today has an excellent chance of avoiding serious disability and deformity. No available pharmacologic agent can permanently alter the course of the disease, and no pharmacologic agent can preclude the need for a balanced program emphasizing moderation, rest and constant attention to physical therapy.*

Early synovectomy is enjoying increasing popularity although the long-term benefits have yet to be established.

The several drugs now undergoing trial hold little promise of materially altering the management of rheumatoid arthritis in the near future. The skills of physician, surgeon, and physiatrist must be brought to bear to provide optimal care.

ANY REVIEW OF the advances in the treatment of rheumatoid arthritis tends to wrongly emphasize the pharmacologic "advances"—the latest wonder drugs—at the expense of the time honored and time proven medical and surgical pillars of management. This mistaken emphasis takes place not only on the written page but more importantly in the mind of the physician and patient alike. Our fascination with drugs, especially new drugs, is endless.

The effect of this disease on the patient's life is almost always considerable. Rheumatoid arthritis is a chronic and recurrent disease which often alters all aspects of the patient's life—his work, his family, his leisure—requiring him to live with pain and progressive disability. The patients tax our technical skills and in addition they tax the human resources of the physician in a unique way. The increasingly complex skills of modern medicine demand a team approach by the physician, surgeon, and physiatrist.

Goals of Therapy

The goals in treatment of rheumatoid arthritis clearly reflect our inability to cure the disease. They are: (1) The prevention of deformity, (2) the relief of pain, (3) the maintenance of the ability to work at home or at the office, and (4) the correction of deformities.

How do we go about reaching these goals? The following two principles are emphasized:

1. Teach the patient to live with a chronic disease.

2. Use skillfully all available medical and surgical modalities.

The first principle cannot be overemphasized.

This material has been received by the Office of The Surgeon General, Department of the Army, and there is no objection to its presentation and/or publication. This review does not imply any indorsement of the opinions advanced or any recommendation of such products as may be named.

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Total resignation and passive acceptance does not serve the patient well. A thorough knowledge of the disease and of the methods of therapy available to combat it is a first step in patient education. In the initial months of the disease neither the physician nor the patient has a clear idea of how aggressive the disease may be.

It is important to note here that what we learn in medical school about rheumatoid arthritis and what we read in the textbooks generally emphasizes the extreme case. Many patients have latex-positive disease over many years without missing a day's work, without deformity, and without the need of anything other than aspirin and moderation in their living. If many physicians have a skewed notion of this disease, many more patients do. It is essential to sit down with the patient and point out that although, as with many conditions, the cause is unknown, it is certainly not the result of something they did or did not do—like running around without a coat or like "running around."

It is well to point out that, again as with most diseases of undetermined cause, there is no specific cure. The patient should realize that the natural history of the disease generally brings both spontaneous remissions and exacerbations lasting for weeks or months. The patient can be told that measures are available today that were not available years ago and that with good care and great effort on the patient's part to cooperate, there is little chance that he will be seriously crippled or unable to work. This knowledge is the cornerstone of therapy and generally must be given over several visits as the rapport between physician and patient develops. From this knowledge grows the determination and perseverance that makes many patients with rheumatoid arthritis so remarkable. This attitude on the part of the patient, coupled with an optimistic, aggressive and sympathetic attitude on the part of the physician, makes for effective management.

Supportive Measures

In the United States it is rare to see a patient whose diet is inadequate. Occasionally it is necessary to help a patient control obesity which, untreated, increases the wear and tear on affected joints. In the absence of obesity, a balanced diet without vitamin supplementation is recommended. Rest is a more important consideration and one that is frequently given insufficient attention. A mid-day nap at home or at work may obviate the need for a more powerful and hazardous pharmacologic agent. Fresh air, regular hours, early to bed and early to rise, and a cheerful home all make this disease more tractable. If a young patient's occupation involves appreciable manual labor, early consideration must be given to retraining in a new occupation more compatible with his disease.

Physical Therapy

Maintenance of function of all joints is a primary goal. Physical therapy provides the means. Prevention is the keynote. Simple range of motion exercises, religiously practiced, can prevent ankylosis. Heat applied by means of moist packs, soaks or paraffin will be effective in reducing stiffness and pain and hence enhance the ease with which complete range of motion can be obtained.

The patient must be carefully instructed in the use of both heat and exercise. This is best accomplished initially under the daily supervision of an experienced physical therapist. Although the majority of subsequent physical therapy can and should be done at home, supplemental sessions perhaps every two weeks with the therapist are advisable. The physician, too, must repeatedly inquire about and urge the patient's use of these daily exercise sessions. The actual program will vary with the patient's daily habits and the location and severity of rheumatoid involvement. As a rule the patient is instructed to start the day with a hot soaking in the tub for 20 to 30 minutes. Following this, each joint is carefully moved through a complete range of motion several times. Whenever possible the heat and exercise session should be repeated again later in the day.

When joints become severely inflamed the natural tendency is to avoid motion. This immobility accompanied by increased comfort in the position of moderate flexion promotes rapid ankylosis. The physical therapist must move the joint through the full range of motion (R.O.M.) while the patient is either totally relaxed (passive R.O.M.) or after the patient has accomplished the greatest possible motion on his own (passive-assistive R.O.M.). The nursing staff should assist the patient in regular changes in position implementing the full range of motion at 30 to 45-minute intervals. This should be continued until these activities are readily assumed by the recovering patient. Splinting of an acutely inflamed joint will usually provide relief of pain and also serves as a means of maintaining and improving extension.

It is wise to continue a prophylactic program of physical therapy even when the disease is relatively quiescent. Not uncommonly, "smouldering" inflammation in a joint will result in insidious loss of motion. Once loss of motion has occurred, there may be partial reversibility with intensive physical therapy and the application of gentle traction or with resting-splints at maximal attainable extension. Except with mild early loss of motion, complete restoration is essentially never attainable and one must guard ever more closely to avoid further loss of motion.

The occupational therapist can provide assistive devices, such as large handled tableware, to make everyday living less difficult. Handicrafts such as weaving encourage the arthritic in motion and strength building exercises. A cane or crutches are occasionally useful to minimize the trauma to involved weight-bearing joints.

Drug Therapy

Concomitant with the prevention of functional loss, the best possible control of inflammation and thereby of cartilage and bone destruction must be accomplished. None of the currently available pharmacologic agents can be said permanently to alter the course of the disease. Gold salts and antimalarials are capable of inducing remissions and thereby of temporarily altering the course of the disease. Salicylates, indomethacin, phenylbutazone, corticosteroids and immunosuppressive agents may relieve pain and suppress inflammation without inducing a true remission.

Salicylates are of considerable value in almost every case of rheumatoid arthritis and often are the only pharmocologic agent that need be added to the basic program of rest and physical therapy. When troublesome activity persists despite use of these drugs, a several weeks' course of indomethacin or phenylbutazone may be considered. In the more severe and persistent case, consideration of long-term therapy with gold salts or antimalarial drugs is warranted. Corticosteroids are reserved for the most refractory and acute problems. The merit of immunosuppressive drugs and certain other new anti-inflammatory and analgesic agents has yet to be established.

Salicylates, traditionally used in the treatment of rheumatoid arthritis for their analgesic properties, also have an anti-inflammatory effect.[1-5] Withdrawal of salicylates during meperidine analgesia evokes an aggravation of swelling and pain that is relieved when salicylates are readministered. It is primarily for this anti-inflammatory effect that salicylates should be used. The usual starting dose of 12 to 16 5-grain tablets of aspirin daily in divided doses may be increased to 18 to 24 tablets. Heartburn and indigestion can be expected but often improve as therapy is continued and may be minimized by giving the aspirin with meals. The appearance of tinnitus, decreased hearing, blurred vision or lightheadedness herald toxic levels and are useful endpoints for clinical titration.

Rarely a patient will not experience these early signs of salicylate toxicity, and the first manifestation will be the more ominous nausea and vomiting. Therapeutic blood levels range from 20 to 25 mg per 100 ml. Serious toxicity usually appears at a level of about 40 mg per 100 ml manifested by central hyperventilation, followed by repiratory alkalosis and metabolic acidosis. It is an unusual patient who is unable to tolerate therapeutic dosages of aspirin. Problems that may be encountered are for the most part uncommon or mild. Gross gastrointestinal hemorrhage occurs infrequently, but a certain degree of insidious blood loss from the gastrointestinal tract is common and may contribute to the anemia of rheumatoid arthritis.[6] Normal persons will have some prolongation of the bleeding time of no clinical significance. A recent report has incriminated aspirin in five cases of marrow depression with pancytopenia.[7] The possibility of allergic sensitivity must be considered; most common manifestations include the aggravation or precipitation of bronchial asthma and the appearance of urticaria.

Buffered aspirin U.S.P. is sometimes less irritating to the gastrointestinal tract. Many coated aspirin products are erratically absorbed and must be used with caution. Combined with the salicylates, dextropropoxyphene (Darvon®) enhances analgesia. Administration is simplified by utilizing a plain 65 mg capsule every four hours as needed for pain. Codeine and the other narcotic analgesics are best avoided altogether. The addition of other compounds to aspirin offers no demonstrated advantage.

When a patient does not respond satisfactorily to a basic program, including the use of salicylates as described, the next consideration should be reevaluation of the manner in which the basic program has been followed. Often admission to the hospital for two weeks of full basic treatment will result in remarkable improvement. This serves as both a therapeutic measure and learning experience for rheumatoid patients.

If in spite of careful attention to the foregoing program, control remains inadequate, the addition of indomethacin may be considered. While indomethacin is certainly not always effective, it does generally compare well with salicylates in comparative effects on grip strength, number of tender joints, and reduction of sedimentation rate, and it may be useful in the patient who cannot tolerate salicylates.[8] Twenty-five milligrams twice daily with meals and coffee may be gradually increased to 50 mg three times daily. Those amounts will be tolerated by most patients. With these precautions, the common side effects of headache and upper gastrointestinal distress will seldom require discontinuation of the drug.

Other side effects are less common but include depression, urticaria, purpura, liver function or marrow depression, aggravation of essential hypertension, and deterioration of diabetic control. Most rarely the arthritis may be aggravated by indomethacin.[9] Unexpected and sudden death in four children taking indomethacin has been reported.[10]

Phenylbutazone and oxyphenbutazone have perhaps a more predictable analgesic and anti-inflammatory effect but are associated with greater toxicity.[11-17] Four hundred mg a day of either drug for the first two to four days with gradual reduction to 100 mg once or twice daily is recommended. Weekly blood cell counts and clinical evaluations are indicated for at least the first two months and then every two to four weeks thereafter. The limiting side effects include gastrointestinal symptoms ranging from mild irritation to severe ulcerogenesis, hepatitis, dermatitis, stomatitis, headache, vertigo and edema. These drugs may extend the prothrombin time in patients taking anticoagulants. Of most concern are the rare but grave hematologic dyscrasias ranging from leukopenia to agranulocytosis and aplastic anemia. Forty-eight cases of agranulocytosis, ten of them fatal, occurring between 1951 and 1959 have been summarized.[17]

If activity of the disease requires frequent courses or high dosage of indomethacin or phenylbutazone, the physician should consider the use of gold salt therapy.[18] This form of treatment also carries appreciable risks and is generally to be avoided in the patient with advanced disease and pronounced destruction of joints. If a complete blood cell count, platelet count, urinalysis and BUN determination are within normal limits, a test dose (10 mg) of a soluble gold salt such as Myochrysine® or Solgonol® is given. A blood cell count, platelet count and urinalysis are done before each injection and the patient is examined as well as asked about skin or oral reaction. The second week's test dose is increased to 25 mg, and finally doses of 50 mg are administered weekly as the therapeutic trial continues for approximately 20 weeks.

It is usual to see little or no response to gold therapy during the early weeks of therapy, and treatment should not be discontinued because of lack of response until approximately four months have elapsed. About 80 percent of rheumatoid patients will experience at least some benefit, and complete remission is induced in about 20 percent. Until recently it was the practice to discontinue gold salt therapy after an arbitrary period or after a remission had been induced. More recently the benefits of continued monthly injections for an indefinite period have been emphasized. If an exacerbation should occur during such maintenance therapy, the patient may once again be given 50 mg weekly for several weeks. If a remission has been maintained for two or three years, consideration should be given to discontinuing therapy, with the reservation that beginning it again, with the same precautions initially observed, may be necessary.

If contraindications to gold therapy are present or when a satisfactory response is not obtained, the antimalarial agents provide another avenue of approach.[19] Chloroquine (Aralen®) in a daily dosage of 250 mg or hydroxychloroquine (Plaquenil®) in a daily dosage of 200 mg must be given for four to six weeks before a clinical response can be expected. When a response is obtained, it may range from a mild amelioration of symptoms to induction of a remission. If significant clinical improvement is not evident after six or eight weeks, it is probably best to discontinue antimalarial therapy. When a remission is obtained, the antimalarials are usually continued for a year unless significant side effects occur.

Benign dermal or gastrointestinal reactions to the antimalarials, and rarely more serious complications, may be encountered. Psoriasis is readily exacerbated by antimalarial drugs and constitutes a contraindication to their use. Ocular side effects from the antimalarials include reversible corneal lesions. These are usually asymptomatic but there may be some blurring of vision. More serious are retinal lesions which have been known to appear or progress even after the drug has been discontinued and which may lead to blindness. Thus, patients taking the antimalarial agents should have ophthalmologic examination every three to six months for field of vision and color testing as well as retinal and corneal visualization. Most of the retinal complications have followed the use of chloroquine in dosages greater than 250 mg daily for periods longer than a year. For this reason, Plaquenil is the drug most commonly used. It is necessary to inform the patient that rarely impairment of vision may occur; the equally serious potential toxicity of alternative drugs should also be appreciated.

The problems incurred by the administration of corticosteroid drugs in the therapy of rheumatoid arthritis are widely known. Nonetheless, the appearance of iritis or of scleromalacia perforans—a rheumatoid nodule forming in the sclera—makes the use of steroids mandatory. Dosage must be titrated to levels adequate to control the complication.

More commonly the indication for corticosteroids is that of inadequate control of systemic disease by safer measures. In that case, steroid therapy should be aimed at adequate control, not total amelioration of symptoms. Using small doses, usually 5 to 7 mg of prednisone daily, adequate control can generally be obtained without inviting serious secondary steroid effects and with a minimum of adrenal-pituitary inhibition. Newer synthetic steroids appear to offer no particular advantage.

Alternate day steroid therapy is rarely tolerated by the rheumatoid arthritic and is generally more pertinent to other situations in which higher dosage of steroids is indicated. Intermittent intra-articular steroid injections are valuable in the control of persisting inflammation in isolated joints. A crystalline suspension of prednisolone — tertiary butyl acetate (Hydeltra TBA) is less absorbable and hence its effect may be prolonged. Since it is a crystalline preparation, some patients may have an acute but brief flare of joint pain following an injection. When necessary this can be prevented by incorporating a small amount of a soluble corticoid in the joint injection. The amount of corticosteroid to be used for intraarticular injection will vary with the size of the joint; usually 2 ml of Hydeltra TBA (40 mg) for large joints such as the knee, and 0.4-0.5 ml (8 to 10 mg) for an interphalangeal joint.

Patients who have surgical operations while receiving or within a few months following corticosteroid therapy will need additional steroids to avoid addisonian complications.[22] Generally 200 mg of hydrocortisone acetate is given parenterally 12 hours before and the same amount two hours after operation, followed by 100 mg ten hours later and decreasing daily doses until the preoperative treatment level has been reached.

Not uncommonly after a patient has been taking steroids for some time, a partial or complete withdrawal is feasible, and almost invariably will be successful if done slowly and cautiously. Rapid withdrawal usually causes a rebound flare of the arthritis and symptoms of Addison's disease, with the result that the patient's dependence on steroids is only enhanced. Withdrawal as slow as a 1 or 2 mg reduction in dosage each week or even each month is not an unreasonable approach when a more rapid withdrawal cannot be accomplished.

Experimental efforts in the pharmacologic approach to rheumatoid arthritis include:

- New anti-inflammatory drugs.[23-26]
- D-penicillamine or N-acetylcysteine (NAC), which affect the sufhydryl linkage in collagen, rheumatoid factor, and other enzymes and structural proteins.[27,28]
- Attempts to block the deposition of fibrin believed by some to be involved pathogenetically in the rheumatoid lesions.[29-32]
- The immunosuppressive drugs either systemically or locally by intra-articular injection.[33-36]
- The intra-articular administration of gold salts.[37]

The most productive findings appear to be related to the newer anti-inflammatory analgesics. One of these, mefanamic acid, has recently been introduced for clinical use under the trade name Ponstel. Mefanamic acid is reported to be as effective in an appropriate dosage (1.7 gm per day) as 2.4 gm per day of aspirin, 330 mg per day of phenylbutazone or 670 mg of another new agent, flufenamic acid. Yet another new analgesic and anti-inflammatory agent, Ibufenac, (4-isobutylphenylacetic acid) is said to be two to four times as effective as aspirin.[24-26] Experience with these newer agents is insufficient to ascertain their value.

Surgical Therapy

The adjunctive use of surgical operation in the treatment of rheumatoid arthritis is traditionally reconstructive in purpose. The recognition that inflamed and proliferating synovium is the cause of cartilage and bone destruction, possibly via the release of lysosomal enzymes[38] and collagenase,[39] has led to enthusiasm for early synovectomy.[40-42] When it becomes apparent that medical and pharmacologic measures will not prevent destruction of a joint, synovectomy is indicated. This is obviously of greater value before cartilage destruction and the erosion of bone occur, but it also has a place in the partially damaged but functional joint.

Following synovectomy, synovial tissue reappears. This apparently occurs by metaplasia of the surrounding connective tissue and not by regrowth from residual synovium.[43] The newly formed synovial membrane may be involved *de novo* with rheumatoid inflammation within months or years, depending partly on the overall aggressiveness of the disease in the individual patient.

Operation is also indicated when rheumatoid synovitis or peritendonitis threatens tendons, produces Dupuytren's contractures, or leads to carpal tunnel syndrome. When a rheumatoid nodule invades a tendon, rupture is threatened and excision is indicated.

When more serious joint damage has occurred, reconstructive procedures may improve function to a variable degree. At this stage, the consideration is primarily that of function, and if the patient is able to use the involved joint adequately, operation is generally not indicated. In either case, the use of splints, traction, physical and occupational therapy may improve function and should be applied to the greatest possible benefit. After this has been accomplished, the patient is evaluated for surgical correction. The procedures available range from the transposition of tendon insertions to the reconstruction of joint surfaces. Occasionally when overall function can be enhanced by producing an ankylosed joint, arthrodesis is indicated.

Thymectomy was reported done in two patients with the hope of altering the immune reactivity and affecting the course of rheumatoid arthritis, but no significant clinical improvement was observed.[44]

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AVOIDING INJECTION INJURIES

"Injection injuries plague almost every medical practitioner, and pediatricians are not excluded from this potential liability problem. Here we are speaking primarily of radial nerve injury and sciatic nerve injury from injections given in the arm or in the backside in improper locations. I can draw attention to a recent New York case where an injection was given into the backside of a small child and produced direct injury to the sciatic nerve, resulting in a jury verdict of $275,000. Injection injuries are obviously a serious problem every time they occur, and something needs to be done to avoid them altogether.

"I have taken several brief surveys of groups that I have spoken before on past occasions and have found that very few physicians check their office personnel, either at all or periodically, to find out the capability of each person to give injections into proper areas. When doctors do investigate their own personnel, they test only the ability to identify by words the locations where injections should be given. It is not difficult for a nurse to understand that an injection into the arm must be given into the upper third or that an injection into the backside must be given into the upper outer quadrant. But how many of these girls can map out the upper third of the arm or the upper outer quadrant of the backside on a model or on a patient? This is something that needs to be done periodically by all physicians."

—Don H. Mills, M.D., LL.B., Los Angeles
Extracted from *Audio-Digest Pediatrics*, Vol. 14, No. 18, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

Monilial and Trichomonal Vaginitis

Topical Treatment with Povidone-Iodine Preparations

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■ *A regimen of treatment for vaginitis combining the use of a povidone-iodine solution for swabbing, a povidone-iodine vaginal gel for application at night and a povidone-iodine douche for use in the morning, was evaluated in 93 courses of treatment in 87 patients with monilial or trichomonal vaginitis or a combination of both.*

In monilial vaginitis, symptoms were cleared and negative laboratory results obtained in one to three weeks in all 74 courses of treatment. These results were obtained within one week in 52 cases and within two weeks in another 17.

In four of five patients with trichomonal vaginitis, symptoms were cleared within three weeks. In the fifth, negative laboratory results were obtained but a mild discharge persisted at the end of the fourth week.

In 14 courses for combined infections, symptoms were cleared within three weeks in 13, and the pathogens were absent in those patients within four weeks. In one patient the disease did not respond.

MONILIAL AND TRICHOMONAL vaginitis frequently occur simultaneously,[1,2] and control of trichomoniasis with specific agents is often followed by a flareup of moniliasis.[1, 3-5] Whereas trichomonal vaginitis is considered by some observers to be largely a venereal disease,[2,6,7] monilial infection and reinfection of the vagina may issue from the intestinal tract by way of the perineal route.[8,9]

Both *Trichomonas vaginalis* and *Candida albicans* are often found in an apparently healthy vagina.[2,9,10] The triggering mechanisms that turn the saprophytic Candida or the asymptomatic trichomonad into a pathogenic organism have not been fully explained, but reduction of Lactobacilli in the presence of clinical trichomonal or monilial vaginitis has been noted.[5, 11-13] Among predisposing factors suggested for clinical monilial vaginitis are pregnancy, diabetes mellitus,[13,14] and administration of broad-spectrum antibiotics.[10,13,15] Most recently the use of oral progestational contraceptive products has been implicated in the incidence of both monilial and trichomonal vaginitis.[16,17] Antibiotic administration has also been reported to favor the development of trichomoniasis.[2] It has been suggested, however, that the ratio of monilial and trichomonal vaginal infection is shifting to a preponderance of monilia largely as the result of the development of antibiotic therapy.[15,18,19]

Both forms of vaginitis produce symptoms of varying severity, mainly vulvar pruritus, pain, burning sensations, and a vaginal discharge which, in trichomoniasis, is often malodorous.[20] The emotional factor has been especially noted in women with trichomoniasis.[20,21]

In view of the association between monilial and trichomonal vaginitis, local therapy which promises to control both is obviously desirable. Many agents have been tried, but no single method has been satisfactory in all respects. Thus, iodine was at one time used successfully in the therapy of both monilial and trichomonal vaginitis,[22,23] but the concentrations required proved painful on application.[23]

More recently povidone-iodine, a complex of

Submitted 22 May 1968.

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polyvinylpyrrolidone and iodine, has been introduced, and when topically applied it is reported to be microbicidal to both *Trichomonas vaginalis* and *Candida albicans* as well as to a variety of iodine-susceptible microorganisms with potential pathogenicity in the vagina.[24,25] It is reported to be virtually non-irritating, and therefore less likely to cause pain on application.[25] It is available in a variety of forms suitable for use in the vagina, including a solution for direct swabbing, a douche and a vaginal gel.* Since it is water-soluble, it can be removed simply by washing with water, and is thus non-staining to skin and natural fabrics.[25]

A trial of a regimen involving use of the povidone-iodine solution, douche and gel in trichomonal and monilial vaginitis was undertaken.

Materials and Methods

Ninety-four women between 19 and 43 years, with a mean age of 29, were originally included in the trial. Eighty-seven were evaluated. All complained of discharge and nearly all had additional symptoms of vaginitis as well (Table 1); overt physical signs, in addition to discharge, were noted in 58 patients (Table 2). Nine patients were pregnant. Using the hanging drop method for *Trichomonas vaginalis* and culture with Nickerson's medium for *Candida albicans,* the condition was diagnosed in the original 94 patients as moniliasis in 71, trichomoniasis in seven, and both concomitantly in 16. Six patients were treated for second episodes, presumably due to reinfection. In three cases the second episode occurred four to five months after therapy, and in two cases—one in a patient with suspected gestational diabetes—five weeks after therapy. The remaining recurrence of moniliasis was three weeks after cessation of therapy and it coincided with the return of the patient's husband after a month of absence. These recurrences brought the number of treatments initiated with the regimen under study to 100, of which 76 were for moniliasis, seven for trichomoniasis and 17 for a combination of the two conditions.

Following initial examination and taking of diagnostic smears, the vagina and cervix were painted with the povidone-iodine solution. The patient was instructed to apply one applicatorful of the povidone-iodine gel (approximately 5 gm) at bedtime and to douche next morning, using a dilution of 2 tablespoonfuls of the povidone-iodine douche in 1 quart of warm water. This course was followed for six nights and mornings. On the seventh day the patient reported to the office, where symptoms were again noted and smears obtained for laboratory determination.

TABLE 1.—*Distribution of Symptoms, 93 Cases of Vaginitis in 87 Patients*

Symptoms	*Monilial*	*Trichomonal*	*Trichomonal and Monilial*
Discharge only	3	1	1
Discharge and itching	27	3	7
Discharge and burning	3	—	—
Discharge and pain	1	—	—
Discharge, itching, and burning	21	—	4
Discharge, itching, and pain	3	—	1
Discharge, itching, burning and pain	16	1	1
TOTALS	74	5	14

The course of treatment, consisting of the douche and gel regimen, was continued, with weekly examinations, for four weeks, or less if symptoms were cleared and laboratory results were negative. Patients were instructed to avoid sexual intercourse, or to engage in it only with the use of a condom by the sexual partner, during the course of treatment.

Treatment was recorded "effective" when symptoms were cleared and laboratory findings negative upon completion of the prescribed course. It was recorded "ineffective" (for purposes of the study) where symptoms persisted, or laboratory results were positive, upon completion of the full course of treatment.

Results

Seven patients did not complete the prescribed course of therapy and were not included in the evaluations. Results for the remaining 93 completed treatment courses (87 patients) are shown in Tables 3 and 4. The povidone-iodine regimen was evaluated as effective in 100 percent of treat-

TABLE 2.—*Pertinent Physical Findings, 93 Cases of Vaginitis in 87 Patients*

	Diagnosis		
Erythema or lesions of:*	*Moniliasis*	*Trichomoniasis*	*Moniliasis and Trichomoniasis*
Vulva	23	—	—
Vagina	3	1	1
Cervix	12	1	8
Vulva and vagina	1	1	1
Vulva and cervix	3	—	—
Vagina and cervix	—	—	2
Vulva, vagina and cervix	1	—	—
TOTALS	43	3	12

*Punctate areas, erosion, excoriation, inflammation, irritation.

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*Betadine Solution, Betadine Douche, and Betadine (Povidone-Iodine) Vaginal Gel, The Purdue Frederick Company, Yonkers, N. Y.

ments for monilial vaginitis, in four out of five treatments for trichomonal vaginitis, and in 93 percent of treatments for combined infections.

Treatment was recorded as ineffective in one patient with trichomonal vaginitis in whom laboratory results were negative at the end of treatment but a mild discharge persisted, and in another with mixed infection which was not controlled within four weeks.

In the 74 evaluated courses of therapy for monilial vaginitis, symptoms were cleared and negative laboratory results obtained within one week in 52 patients, within two weeks in 17 and within three weeks in five.

Of the nearly 250 presenting symptoms recorded for all patients, 200 were reported as severe and the remainder as mild (Table 3). Nearly 90 percent of the severe symptoms were cleared within two weeks. Of the 50 mild symptoms, 45 were cleared within the first week and the other five the second week.

Results with the povidone-iodine regimen were evaluated as superior in 12 of 13 patients previously treated with other agents, and as about the same in one.

Seven of the nine pregnant patients had monilial vaginitis. Symptoms were cleared and laboratory results negative by the end of the first week in six of them, and by the end of the second week in the seventh. Two pregnant patients had trichomoniasis and moniliasis. Symptoms were cleared and laboratory results negative within three weeks in one and four weeks in the other.

Of 53 patients who reported "immediate relief" following the swabbing of the vagina with the povidone-iodine solution, 20 had complained of itching before therapy; 16 of itching and burning; three of itching and pain; ten of itching, burning and pain; three of burning only, and one of discomfort due to discharge.

Itching or discharge was still present in the seven patients who dropped out of the study—four after the third week, two after the second week and one after the first week.

Patients acceptance of the povidone-iodine vaginitis regimen was generally good. Of the 94 women initially in the study, 66 voiced no objections to the medication, 17 indicated that the gel application was "messy," five that the procedure was inconvenient, and six that the gel stained their linens.

TABLE 3.—*Relief of Individual Symptoms with Povidone-Iodine Vaginitis Regimen in 87 Patients (93 Courses of Therapy)*

Diagnosis	*Symptom*	*No.*	*Severe*	*Mild*	*Relief Within*			*Not relieved*
					1 wk.	*2 wk.*	*3 wk.**	
Monilial vaginitis	Itch	67	54	13	58	6	3	—
(74 courses of	Burning	40	30	10	34	4	2	—
treatment)	Pain	20	9	11	17	2	1	—
	Discharge	74	68	6	57	13	4	—
Trichomonal vaginitis	Itch	4	3	1	2	2	—	—
(5 courses of	Burning	1	—	1	1	—	—	—
treatment)	Pain	1	—	1	1	—	—	—
	Discharge	5	5	—	—	—	4	1†
Trichomonal and	Itch	13	9	4	9	4	—	—
monilial vaginitis	Burning	5	2	3	3	2	—	—
(14 courses of	Pain	2	2	—	2	—	—	—
treatment)	Discharge	14	14	—	—	5	8	1

Relief of Symptoms by Severity, All Patients

Symptom	*No.*	*Relief within*			*Not relieved*
		1 wk.	*2 wk.*	*3 wk.**	
Itching 84					
Severe	66	52	11	3	—
Mild	18	17	1	—	—
Burning 46					
Severe	32	27	3	2	—
Mild	14	11	3	—	—
Pain 23					
Severe	11	9	1	1	
Mild	12	11	1		
Discharge 93					
Severe	87	51	18	16	2
Mild	6	6			

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*All symptoms were cleared within three weeks in the successful cases.

†Laboratory reports negative, but a mild discharge persisted after four weeks of therapy.

TABLE 4.—*Results in Symptomatology in 93 Courses of Therapy (87 Patients) Following Povidone-Iodine Vaginal Regimen*

		All symptoms cleared within*				*Immediate effect of swabbing of vagina with PVP-I Solution on initial visit*		
Type of vaginitis	*No. Pts.*	*1 wk.*	*2 wk.*	*3 wk.*	*Not cleared*	*Relief*	*No relief*	*Not determined*
Monilial	74	52	17	5	—	49	23	2
Trichomonal	5	—	—	4	1†	—	4	1
Trichomonal and Monilial	14	—	3	10‡	1	4	10	—
TOTALS	93	52	20	19	2	53	37	3

*Laboratory results were negative in all cases where symptoms were cleared, except as indicated. In the successful cases, all symptoms were cleared within three weeks.

†Laboratory reports were negative, but a mild discharge remained after four weeks of therapy.

‡In two patients, hanging drop studies were negative for trichomonads after four weeks of therapy.

Ten of these 28 added that they were pleased with the results of the regimen.

Side Effects

Side effects were minimal. A patient with moniliasis complained of a slightly tender and nonpruritic eruption confined to the plantar and palmar skin following one week of the povidone-iodine vaginitis regimen. This was diagnosed clinically and microscopically as consistent with dermatitis medicamentosum. Medication was discontinued and the eruption cleared within a week. In the week of treatment before the eruption developed, severe vaginal itching and discharge were eliminated and a negative laboratory report was obtained.

Two patients with vulvitis reported "burning," slight in one case, on the first day and first two days respectively of treatment with the povidone-iodine gel. "Burning" was one of the presenting symptoms of these patients before therapy. That it ended after the first two days of therapy may have been due to the treatment.

Discussion

The povidone-iodine regimen—utilizing a solution, douche and gel—was effective, in this series, in the therapy of monilial vaginitis; it appeared to be promising in the treatment of trichomonas vaginitis, as well, but the number of cases was insufficient for definitive judgment. A follow-up report will be submitted after additional clinical experience.

One patient had plantar and palmar eruptions consistent with dermatitis medicamentosum after one week of the test regimen. The signs disappeared upon discontinuance of therapy. Two patients with vulvitis who had "burning" as a presenting symptom, reported persistence of this complaint for one and two days respectively following initiation of gel therapy.

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The Organically Handicapped Child

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■ *The better his understanding of some of the ways in which an organic deficit might affect normal development of the handicapped child, the more able the family physician will be to offer guidance to the family aimed at preventing the development of secondary problems. He can thus be instrumental in helping a child achieve his maximal potential.*

First, it is important to take into account how the parents' emotional and intellectual responses to having a defective child may interfere markedly in normal parent-child relationship. Second, ways in which each deficit will limit a child's exposure to stimuli must not be overlooked. Third, one must consider how a deficit may indirectly distort the normal learning patterns when parents do not make age appropriate demands. Fourth, it is important to understand how specific interference in the area of language skills may cause further developmental retardation. Fifth, one must be aware of special problems that an organically handicapped child must face in the society outside of the family. Last of all, in an older child, one must consider the need for a full scale evaluation to sort out primary and secondary factors in the picture.

ow Can the Family Physician Help?

A GENERAL PHYSICIAN or pediatrician is frequently confronted by an organically handicapped child and his family. He may see such a child at birth, when there is need for practical information and supportive guidance for the parents. There may soon be questions about child rearing, about future special schooling, therapy or the advisability of placement. On the other hand, the physician may not see such a child until later, when the child may appear to function on a developmentally retarded level, or may show deviant patterns of behavior. At this time, questions may arise concerning: (a) The degree of actual organic deficit; (b) whether a basic mental retardation or other organic deficit is also present; (c) the part played by emotional factors—whether these are secondary to the organic problem or seemingly independent of it.

If a physician is to give optimal help to an organically handicapped child and his family, he should have an overall view of the special problems that these children encounter in their development. At times, the assistance of others may be indicated for counselling or adequate evaluation of these complex situations. But, by maintaining a position of primary responsibility to the family and coordinating all of the care, the family physician can avert many secondary problems for the child. Furthermore, he can prevent the family from feeling (and sometimes becoming) lost in the shuffle of experts.

We will confine our presentation primarily to children who are blind, deaf, or handicapped in such a way as to limit locomotion or the acquisition of speech. However, much of what follows is also applicable to any child whose defects interfere with his own development or alter the normal responses to him, or feelings about him, of those in his immediate environment. A child with an organic deficit has the same basic physical, emotional, and intellectual needs as do all children. Because of his deficit and the special needs and problems that it creates, the basic needs may not be adequately met.[1]

Based on our experience that families of children with special handicaps need assistance at every stage, we have approached the problem according to the chronological sequence of the parent-child experience and the physician oportunity, rather than focusing on different handicaps. The latter approach would not only involve unnecessary repetition, but would also place undue importance on the specific handicap instead of on the "total" child.

Parent-Child Relationship

Frequently the parents' response to a deficit and its subsequent manifestations serve to disrupt the very beginnings of the parent-child relationship. Following are some points which may be critical in determining whether a general affective deprivation may then compound the original damage.

1. Have the parents been able to come to grips with their own sadness, disappointment, guilt and anger about producing a defective child?[2] Have they been overcome by a feeling of helplessness? Have they become depressed and withdrawn from the child, or, on the other hand, over-identified with him? What unresolved conflicts in each parent or in the marital relationship have been activated by their producing a "defective" child?

In this primary situation of parental despair, the

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Submitted, revised, 6 August 1968.

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physician can play a key role by helping parents through a real "mourning" period. He can convey to them his understanding and acceptance of their feelings and help them realize that having reactive feelings does not mean that they are "bad" parents. He can thus "free" them to function more fully in meeting the reality situation.

2. How well have the parents understood the deficit? Have they been able to form realistic expectations for the child, his capacities, his special needs and how to meet them? Have they been confused by misinformation from newspapers and magazines?

Here the physician can play a role as educator. Information that will clarify causes and prognosis will have to be given to the parents again and again, as they become more able to think objectively about the total situation. It is important for the family physician to follow up on his explanations, to appraise how much the parents have really understood and how much they continue to cling to desperate hopes about their child still being normal or about some miraculous cure being found.

3. How well have the parents been able to focus on the whole child, to warmly accept him as an individual and not become preoccupied with his deficit and with constant evaluation of it? Have their normal impulses to reach out and respond to him been interfered with by this preoccupation? In this connection it is important for the physician to stress that the role of parents is to help any given child to be happy and to reach his *own* potential.

4. Have there been difficulties in setting limits? It is disturbing for parents to put further restrictions on a child already defenseless from the limitation of his handicap. A child with language retardation may appear too young to understand. With deaf children, there are specific problems in trying to convey shades of meaning rather than just to give "absolutes." It may thus be very difficult to communicate information about acceptable customs of behavior. In children with any organic deficit complicated by convulsions, it is very frightening for parents to set limits when a temper tantrum may trigger a seizure.

In this matter of limit-setting the physician can often be specifically helpful. For instance, he can consider with the parents which restrictions are essential and which can be handled by environmental manipulations. He may also be able to help them work out special means to convey training ideas to the child, (for example, through pictures to a deaf child).

5. Have the parents been able to help a child become independent? It is difficult to convey a feeling of separateness when in reality the parent must so often act and speak for a child with a special handicap.[3] How much infantilization and unnecessary over protection has there been? This problem is of course closely interwoven with the problem of limit setting. The physician can reassure parents that it is necessary for the child's normal personality development that he be allowed the experience of some frustration. Every wish must not be immediately gratified. The child should also be given chances to give to others, not only to receive. A normal atmosphere must be created which includes peer relationships and their demands for compromise and adjustment.

6. How well have the parents been able to handle the realistic problems which ensue from having a defective child in the family? This would include consideration of adequate rest for the mother and time for herself, opportunity for the parents to have sufficient time with other children, means of meeting the unusual financial burdens, questions about advisability of future pregnancies, etc. While the physician himself may be able to point out the existence of such problems and to offer answers to many, he may also wish to direct parents to appropriate agencies for specific guidance in plans for baby sitters, financial loans, and such matters.

7. What is the impact of a deficit on a child's approach to the world? Early in life he senses his parents' concern, for he is born into an atmosphere of anxiety. There may be specific aftermaths of diagnostic procedures and hospitalizations. The subject of his deficit may be taboo within the family, much as the subject of sex is often taboo. The physician can be helpful by discussing this aspect of the problem with the parents and perhaps by assisting them in extending their explanation to the child. Such explanations will need to be repeated many times to parents and child and will become more detailed as the child matures.

8. Have the parents found some means of communicating to make as relaxed and close a "give and take" relationship as possible? Has the essence of communication been maintained, even if the means are not usual? A mother can feel very frustrated if she does not get the usual responses

from a child. A blind child may appear passive and unresponsive, but may actually be quiet and listening. A mother may not know how to maintain and build a relationship with him since she is not able to share visual experiences. She may become discouraged and isolate herself from him.[4] Although sign language is the natural way to communicate with deaf children, parents have often been discouraged from using it and feel tremendous guilt about using anything other than verbal communication. Hence, they may end up without any real means of communicating.

The physician can encourage the parents to communicate with their child in any way that seems natural. In so doing he will not only be following the dictates of his own common sense and that of the parents, he will also be in line with the findings of contemporary research, which is showing that deaf children learn best when verbal and sign languages are combined. The important thing is to communicate, using all the sensual modalities that are possible. Thus, hand signing is important with the deaf, touch and sound with the blind, etc.

Exposure to Stimuli

Each type of deficit will limit the child's exposure to stimuli in its own specific way. The consequences will be determined by the nature and extent of the deficit as well as by the time of its occurrence—that is, whether it is congenital or results from a later illness or accident.

A blind child will not be aware of the existence of an object before he can feel, hear, smell or taste it. Before he has locomotion, he will be aware only of objects in his immediate vicinity. On the other hand, a deaf child will not be attracted by the sound component of people and objects, for example, voices of familiar people, music, automobiles, and the like.

Children with physical defects, such as cerebral palsy, may have pronounced interference with their locomotion and with their ability for manual exploration of their environment. Furthermore, any defective child may be kept away from things and people; objects may be removed from his reach; or he may be physically confined. He may also be underexposed to the environment because he acts or communicates like a child far younger than his age.

The defect may interfere in a child's ability to select, interpret, or make meaningful wholes from stimuli. A child may actually cease to pay attention, or try to interpret stimuli because he is unable either to understand them or to turn them into meaningful action for himself.

An inherent difficulty in symbolic self-expression, such as exists in aphasia, will limit a child's verbal exploration of his environmental and verbal relationship with people in it. (This will be further discussed later.)

The alert physician can start counselling families as early as possible about preventing stimulus deprivation. Practical advice can be given about how to allow and encourage the child to come into contact with the environment. In regard to a blind child, for instance, parents must understand that, although he is quiet, it is important not to leave him to himself too much; that verbal may have to substitute for visual stimuli; that he has need for safe areas that he can be left alone to explore. Similarly, with a deaf child, parents may need help in how to use visual for acoustic stimuli, (for example, waving a hand rather than calling to a child, and exaggerating facial expressions). For any child limited in locomotion, specific ways may have to be planned to bring the environment to the child.

Learning Patterns

A deficit may indirectly affect all normal learning patterns. The beginning of all learning occurs within the mother-child relationship. In a handicapped child, general development, including motor, may be slow because a child has a hard time sensing the mother's active participation and enjoyment in these activities.[4] Furthermore, motor development may be normal until creeping begins. At this time there is frequently a striking development arrest, largely because there is inadequate visual or acoustic stimulus to walk, dependent on the specific handicap. Age-appropriate activities may not be demanded of a handicapped child. He may be denied solid foods until far past his natural biting age, and thereby retain a passive feeding role. There may be a permissiveness toward messy eating habits, and a late weaning. Toilet training may be postponed, and the parents may encourage passivity by dressing a child far past babyhood, without stimulating his active participation.[1]

Again the alert physician can forewarn parents about these difficulties. They should be helped to find appropriate means to encourage development and make age-appropriate demands on the child.

Later they can be helped to find necessary special educational methods.

Language Skills

Specific interference may occur in the area of language skills. A mother may acquire the habit of using less verbal language with any handicapped child, relying mainly on sign language. This may make sense with a deaf child, but not with one who has normal hearing. More, the mother may expect less of the child in the way of complete responses.

For a blind child, imitation of sound is one of the main means of contact in the early years. Later, talking may become more parroting than actual communicating.[4] Since there is difficulty in acquiring the concept of objects and people from a perception of them, the development of speech is not naturally stimulated by a wish to bring back the lost object or to name objects. This is especially true before locomotion is developed.[5] At times a blind child may be exposed to bits of speech that make no sense because he cannot see the visual accompaniments, (for example, hearing one side of a telephone conversation).

For a deaf child there is a tremendous problem in grasping the spirit of language and not just becoming bogged down in the formal structures.[6] He will never "hear" grammar and word choice — it must come to him as a learned foreign language. Hence, a reasonably high intelligence is a prerequisite for the development of verbal language in a deaf child, as well as early language training.

Without language, children will function on an increasingly retarded level, both from a lack of speech *per se,* and from the secondary effect on personality development resulting from inadequate verbal communication. In an article on the role of verbalization in early childhood, Katan[7] mentioned some of the consequences of inadequate verbalization. These tend to allow the persistence of primitive ways of relating to the world, of expressing feelings, and of distinguishing wishes and fantasies from reality. Furthermore, without adequate language there will be no way for a child fully to understand his deficit or to express his feelings and anxieties about it. If there is limited verbal ability, there will be great problems in learning about sex. This is even more pronounced if there is a sensory defect like blindness or deafness, where media other than visual or verbal must be used.

It must be remembered how essential verbal language is to normal mental growth. A toddler, with his many questions, uses language as an exploratory tool. An older child gains information about society, its customs, dictums, prohibitions and the like, at least in part from conversation. All this knowledge is necessary for individual functioning as a mature, independent member of society.

Language is used in establishing confidence, relating to peers, and forming a sense of identity. During the school period, language is something to be dominated and exploited. This is well illustrated in secret codes, verbalism, rationalizations, "as if" roletaking, moralizing statements, expressing anger in "under the breath," jokes, etc.[8]

When effective verbal language is retarded or not possible, substitute means of relating to the world and expressing wishes and feelings must be found. Here the physician may play his most important role by placing parents in contact with organizations designed especially to help with such crucial problems. Societies and agencies for the deaf, for the blind, and the like have developed educational films and many educational materials, which will help parents find optimal methods for relating words to objects and to abstract concepts and for encouraging whatever verbal language is feasible.

Community Experience

One must consider some special problems that an organically handicapped child must face in the society outside of his family:

- Can his special educational needs be met? Must he travel to another community, and possibly be separated from his parents, to meet them?
- How much does physical mobility limit his participation in society? How well can this be compensated for by special devices or people or activities coming to him?
- Can he find a group to identify with? Much is written about the choice that a deaf child must make between belonging to the deaf or the hearing community.[9]
- How much are the actions of his local community influenced by their suspicions, fears and prejudices? Do they show only pity, rather than true understanding? For example, society may treat the hard of hearing child as being preoccupied, inattentive, stupid, queer, self-centered.[6]
- Is the child permitted to become an independent, contributing member of society? Since, in

the early years, a handicapped child has had to make much of his contact with society second hand via his parents, has he eventually learned sufficient skills and gained adequate confidence so that he can relate to society by himself?

The physician should broach these subjects with the family before they become actual issues to be faced. Here, too, the physician may be of great assistance through steering the family to proper community agencies.

Comprehensive Evaluation

When a deficit is recognized at birth, or in the neonatal period, each problem can be dealt with as it arises. However, if a handicap is not recognized until a child has reached the age of three or four years, the total picture may be very puzzling.

With less than an optimal environment, it is not surprising that some children with organic defects should become "pseudo-retarded" or emotionally or functionally limited—handicapped far beyond the original deficit. The picture may become so complex and irreversible that it will be difficult or almost impossible to appraise developmental level and to ascertain whether a primary mental retardation had also been present.

In such instances, the family physician should take the initiative in bringing in appropriate consultants or in referring to a qualified multidisciplinary team for comprehensive diagnosis. Even a team which is experienced in evaluating verbally limited children,[10] may wish to defer diagnosis until better opportunities have been provided for a child. Missed developmental opportunities may have to be made available, and specific educational methods of therapy tried, before the etiologic factors can be unraveled. An infantilized child may blossom if encouraged to become independent. A deaf child may emerge from depressed isolation when provided with a hearing aid. In such circumstances, diagnosis on follow-up study will be different and more valid than a first assessment.

Conclusion

There are many ways in which an organic deficit may interfere in normal development. It may act through disrupting the normal parent-child relationship or by limiting a child's exposure to stimuli. It may be damaging primarily because no adequate compensatory means have been provided. Failure in language skills may lead to secondary developmental retardation.

Crucial to his optimal evolution will be the strength and emotional health of a child's parents, their response to him as a defective child, how ingenious they are at overcoming obstacles created by his deficit, how much they have been able to allow and encourage his independence, and how well they have been able to help him develop effective communication, ideally on a verbal level. The way in which society accepts and helps the defective child will become increasingly important to his chances for growth.

The family physician or someone working with him can play a vital role in long term supportive counselling to the parents. This should be focused on helping them work through their feelings about their defective child so as to "free" their normal parental impulses, and on facing the realistic problems of child raising so as to approximate normal conditions. If it becomes necessary to refer to specialists or arrange for a full scale comprehensive evaluation, he should retain the role of primary responsibility to the family. He can thus avoid fragmentation of the child's care.

In summary, the family physician's understanding of the complexities involved in the development of an organically handicapped child may make the critical difference in helping the child achieve his own maximum potential for full and happy living. The physician need not be an expert in all the problem areas surrounding the child. But he should recognize when expertise is required, and he should know how to direct the parents toward appropriate help.

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Marijuana in Medic

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CANNABIS INDICA, CANNABIS sativa, Cannabis americanus, Indian hemp and marijuana (or marihuana) all refer to the same plant. Cannabis is used throughout the world for diverse purposes and has a long history characterized by usefulness, euphoria or evil—depending on one's point of view. To the agriculturist cannabis is a fiber crop; to the physician of a century ago it was a valuable medicine; to the physician of today it is an enigma; to the user, a euphoriant; to the police, a menace; to the traffickers, a source of profitable danger; to the convict or parolee and his family, a source of sorrow.

This paper is concerned primarily with the medicinal aspects of cannabis.

Cannabis in Medicine Before 1800

The Chinese emperor Shen-nung is reported to have taught his people to grow hemp for fiber in the twenty-eighth century B.C. A text from the period 1500-1200 B.C. documents a knowledge of the plant in China—but not for use as fiber. In 200 A.D., the use of cannabis as an analgesic was described by the physician Hoa-tho.[44]

In India the use of hemp preparations as a remedy was described before 1000 B.C. In Persia, cannabis was known several centuries before Christ. In Assyria, about 650 B.C., its intoxicating properties were noted.[44]

Except for Herodotus' report that the Scythians used the smoke from burning hemp seeds for intoxication, the ancient Greeks seemed to be unaware of the psychoactive properties of cannabis. Dioscorides in the first century A.D. rendered an accurate morphologic description of the plant, but made no note of intoxicating properties.[10]

In the thirteenth and fourteenth centuries, Arabic writers described the social use of cannabis and resultant cruel but unsuccessful attempts to suppress its non-medical use.[44]

Although Galen described the use of the seeds for creating warmth, he did not describe the intoxicating qualities of hemp. Of interest is the paucity of references to hemp's intoxicating properties in the lay and medical literature of Europe before the 1800's.[44]

Cannabis in Nineteenth-Century Medicine

The therapeutic use of cannabis was introduced into Western medicine in 1839, in a 40-page article by W. B. O'Shaughnessy, a 30-year-old physician serving with the British in India.[27] His discussion of the history of the use of cannabis products in the East reveals an awareness that these drugs had not only been used in medicine for therapeutic purposes, but had also been used for recreational and religious purposes.

O'Shaughnessy is not primarily known for his discovery of hemp drugs, but rather for his basic studies on intravenous electrolyte therapy in 1831, and his introduction of the telegraph into India in the 1850's.[26]

After studying the literature on cannabis and conferring with contemporary Hindu and Mohammedan wise men, O'Shaughnessy tested the effects of various hemp preparations on animals, before attempting to use them to treat humans. Satisfied that the drug was reasonably safe, he administered preparations of cannabis extract to patients, and discovered that it had analgesic and sedative properties. O'Shaughnessy successfully relieved the pain of rheumatism and stilled the convulsions of an infant with this strange new drug. His most spectacular success came, however, when he quelled the wrenching muscle spasms of tetanus and rabies

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Guest Speaker's Address: Presented as part of a Panel Discussion on Current Problems of Drug Abuse before the Second General Meeting at the 97th Annual Meeting of the California Medical Association, San Francisco, March 23 to 27, 1968.

Reprint requests to: 1840 Grove Street, San Francisco 94117.

st, Present and Future

■ *Medicine in the Western World has forgotten almost all it once knew about therapeutic properties of marijuana, or cannabis.*

Analgesia, anticonvulsant action, appetite stimulation, ataraxia, antibiotic properties and low toxicity were described throughout medical literature, beginning in 1839, when O'Shaughnessy introduced cannabis into the Western pharmacopoeia.

As these findings were reported throughout Western medicine, cannabis attained wide use. Cannabis therapy was described in most pharmacopoeial texts as a treatment for a variety of disease conditions.

During the second half of the 1800's and in the present century, medical researchers in some measure corroborated the early reports of the therapeutic potential of cannabis. In addition, much laboratory research has been concerned with bioassay, determination of the mode of action, and attempts to solve the problems of insolubility in water and variability of strength among different cannabis specimens.

"Recreational" smoking of cannabis in the twentieth century and the resultant restrictive federal legislation have functionally ended all medical uses of marijuana.

In light of such assets as minimal toxicity, no buildup of tolerance, no physical dependence, and minimal autonomic disturbance, immediate major clinical reinvestigation of cannabis preparations is indicated in the management of pain, chronic neurologic diseases, convulsive disorders, migraine headache, anorexia, mental illness, and bacterial infections.

with the fragrant resin. Psychic effects resembling a curious delirium, when an overdose was given, were treated with strong purgatives, emetics with a blister to the nape of the neck, and leeches on the temples.[27]

The use of cannabis derivatives for medicinal purposes spread rapidly throughout Western medicine, as is evidenced in the report of the Committee on Cannabis Indica of the Ohio State Medical Society, published in 1860. In that report physicians told of success in treating stomach pain, childbirth psychosis, chronic cough, and gonorrhea with hemp products.[25] A Dr. Fronmueller, of Fuerth, Ohio, summarized his experiences with the drug as follows:

> I have used hemp many hundred times to relieve local pains of an inflammatory as well as neuralgic nature, and judging from these experiments, I have to assign to the Indian hemp a place among the so-called hypnotic medicines next to opium; its effects are less intense, and the secretions are not so much suppressed by it. Digestion is not disturbed; the appetite rather increased; sickness of the stomach seldom induced; congestion never. Hemp may consequently be employed in inflammatory conditions. It disturbs the expectoration far less than opium; the nervous

> system is also not so much affected. The whole effect of hemp being less violent, and producing a more natural sleep, without interfering with the actions of the internal organs, it is certainly often preferable to opium, although it is not equal to that drug in strength and reliability. An alternating course of opium and Indian hemp seems particularly adapted to those cases where opium alone fails in producing the desired effect.[25]

Because cannabis did not lead to physical dependence, it was found to be superior to the opiates for a number of therapeutic purposes. Birch, in 1889, reported success in treating opiate and chloral addiction with cannabis,[5] and Mattison in 1891 recommended its use to the young physician, comparing it favorably with the opiates:

> With a wish for speedy effect, it is so easy to use that modern mischief-maker, hypodermic morphia, that they [young physicians] are prone to forget remote results of incautious opiate giving.
>
> Would that the wisdom which has come to their professional fathers through, it may be, a hapless experience, might serve them to steer clear of narcotic shoals on which many a patient has gone awreck.
>
> Indian hemp is not here lauded as a specific. It will, at times, fail. So do other drugs. But the many cases in which it acts well, entitle it to a large and lasting confidence.
>
> My experience warrants this statement: cannabis indica is, often, a safe and successful anodyne and hypnotic.[23]

In their study of the medical applications of cannabis, physicians of the nineteenth century repeatedly encountered a number of difficulties. Recognizing the therapeutic potential of the drug, many experimenters sought ways of overcoming these drawbacks to its use in medicine, in particular the following:

Cannabis products are insoluble in water.

The onset of the effects of medicinal preparations of cannabis takes an hour or so; its action is therefore slower than that of many other drugs.

Different batches of cannabis derivatives vary greatly in strength; moreover, the common procedure for standardization of cannabis samples, by administration to test animals, is subject to error owing to variability of reactions among the animals.

There is wide variation among humans in their individual responses to cannabis.

Despite these problems regarding the uncertainty of potency and dosage and the difficulties in mode of administration, cannabis has several important advantages over other substances used as analgesics, sedatives, and hypnotics:

The prolonged use of cannabis does not lead to the development of physical dependence.[11,13,14,24,39,44]

There is minimal development of tolerance to cannabis products.*[11,13,14,24,44]

Cannabis products have exceedingly low toxicity.[9,21,22,24] (The oral dose required to kill a mouse has been found to be about 40,000 times the dose required to produce typical symptoms of intoxication in man.)[21]

Cannabis produces no disturbance of vegetative functioning, whereas the opiates inhibit the gastrointestinal tract, the flow of bile and the cough reflex.[1,2,24,44,46]

Besides investigating the physical effects of medicinal preparations of cannabis, nineteenth-century physicians observed the psychic effects of the drug in its therapeutic applications.[4,27,33] They found that cannabis first mildly stimulates, and then sedates the higher centers of the brain. Hare suggested in 1887 a possible mechanism of cannabis' analgesic properties:

> During the time that this remarkable drug is relieving pain a very curious psychical condition manifests itself; namely, that the diminution of the pain seems to be due to its fading away in the distance, so that the pain becomes less and less, just as the pain in a delicate ear would grow less and less as a beaten drum was carried farther and farther out of the range of hearing.
>
> This condition is probably associated with the other well-known symptom produced by the drug; namely, the prolongation of time.[16]

Reynolds, in 1890,[33] summed up 30 years of his clinical experience using cannabis, finding it useful as a nocturnal sedative in senile insomnia, and valuable in treating dysmenorrhea, neuralgias including tic douloureux and tabetic symptoms, migraine headache and certain epileptoid or choreoid muscle spasms. He felt it to be of uncertain benefit in asthma, alcoholic delirium and depressions. Reynolds thought cannabis to be of no value in joint pains that were aggravated by motion and in cases of true chronic epilepsy.

Reynolds stressed the necessity of titrating the dose of each patient, increasing gradually every third or fourth day, to avoid "toxic" effects:

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*Loewe notes a slight "beginner's habituation" in dogs, during the first few trials with the drug, as the only noticeable tolerance effect.[20]

> The dose should be given in minimum quantity, repeated in not less than four or six hours, and gradually increased by one drop every third or fourth day, until either relief is obtained, or the drug is proved, in such case, to be useless. With these precautions I have never met with any toxic effects, and have rarely failed to find, after a comparatively short time, either the value or the uselessness of the drug.[33]

Concerning migraine headache, Osler stated in his text[11]: Cannabis indica is probably the most satisfactory remedy.[11,28]

Cannabis in Twentieth-Century Medicine

In his definitive survey of the literature and report of his own studies, deceptively titled *Marihuana, America's New Drug Problem,* Walton notes that cannabis was widely used during the latter half of the nineteenth century, and particularly before new drugs were developed:

> This popularity of the hemp drugs can be attributed partly to the fact that they were introduced before the synthetic hypnotics and analgesics. Chloral hydrate was not introduced until 1869 and was followed in the next 30 years by paraldehyde, sulfonal and the barbitals. Antipyrine and acetanilide, the first of their particular group of analgesics, were introduced about 1884. For general sedative and analgesic purposes, the only drugs commonly used at this time were the morphine derivatives and their disadvantages were very well known. In fact, the most attractive feature of the hemp narcotics was probably the fact that they did not exhibit certain of the notorious disadvantages of the opiates. The hemp narcotics do not constipate at all, they more often increase than decrease appetite, they do not particularly depress the respiratory center even in large doses, they rarely or never cause pruritus or cutaneous eruptions and, most important, the liability of developing addiction is very much less than with opiates.[44]

The use of cannabis in American medicine was seriously affected by the increased use of opiates in the latter half of the nineteenth century. With the introduction of the hypodermic syringe into American medicine from England in 1856 by Barker and Ruppaner, the use of the faster acting, water-soluble opiate drugs rapidly increased. The Civil War helped to spread the use of opiates in this country; the injected drugs were administered widely—and often indiscriminately—to relieve the pain of maimed soldiers returning from combat. (Opiate addiction was once called the "army disease".)[41] As the use of injected opiates increased, cannabis declined in popularity.

Cannabis preparations were still widely available in legend and over-the-counter forms in the 1930's. Crump* in 1931 mentioned the proprietaries "Piso's Cure," "One Day Cough Cure" and "Neurosine" as containing cannabis.[44] In 1937 Sasman listed 28 pharmaceuticals containing cannabis.[36] Cannabis was still recognized as a medicinal agent in that year, when the committee on legislative activities of the American Medical Association concluded as follows:

> . . . there is positively no evidence to indicate the abuse of cannabis as a medicinal agent or to show that its medicinal use is leading to the development of cannabis addiction. Cannabis at the present time is slightly used for medicinal purposes, but it would seem worthwhile to maintain its status as a medicinal agent for such purposes as it now has. There is a possibility that a re-study of the drug by modern means may show other advantages to be derived from its medicinal use.[32]

Meanwhile, in Mexico, the poor were smoking marijuana to relax and to endure heat and fatigue. (Originally *Marijuana* was the Mexican slang word for the smoking preparation of dried leaves and flowering tops of the Cannabis sativa plant—the indigenous variety of the hemp plant.)

The recreational smoking of marijuana may have started in this country in New Orleans in about 1910, and continued on a small scale there until 1926, when a newspaper ran a six-part series on the use of the drug.[44] The fad subsequently spread up the Mississippi and throughout the United States, faster than local and state laws could be passed to discourage it. The use of "tea" or "muggles" blossomed into a minor "psychedelic revolution" of the 1930's. Narcotics officers encouraged the enactment of local prohibitory laws and eventually succeeded in bringing about restrictive Federal legislation. In 1937 Congress passed the Marihuana Tax Act, the finale to a series of prohibitory acts in the individual states. Under the new laws, the already dwindling use of cannabis as a therapeutic substance in medicine was brought to a virtual halt. In 1941, cannabis was dropped from the *National Formulary and Pharmacopoeia.*

Around the time of the passage of the Marihuana Tax Act, Walton postulated sites of action for cannabis drugs. Cortical areas, he found, are affected at low dosage, while at high dosage there seems to be a depressant effect on the thalamo-cortical pathways. Hyperemia of the brain appears to be a local phenomenon, unless centers controlling vasodilation might be located in the thalamo-cortical region. Similar possible mechanisms are suggested for the phenomenon of mild hypoglycemia, usual hunger and thirst and occasional lacrimation and nausea.[44]

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*Chairman, Investigating Committee, American Medical Association.

Despite restrictive legislation, a few medical researchers have had the opportunity to continue the investigation of the therapeutic applications of cannabis in recent years. In his study of the medical applications of cannabis for Mayor LaGuardia's committee, Dr. Samuel Allentuck reported, among other findings, favorable results in treating withdrawal of opiate addicts with tetrahydrocannabinol (THC), a powerful purified product of the hemp plant.[1,24]

An article in 1949, buried in a journal of chemical abstracts, reported that a substance related to THC controlled epileptic seizures in a group of children more effectively than diphenylhydantoin (Dilantin®), a most commonly prescribed anticonvulsant.[9]

A number of experimenters, believing that cannabis products might be of value in psychiatry, have investigated the applications of various forms of them in the treatment of mental disorders. Cannabis had been used in the nineteenth century to treat mental illness.[19,25,45,46] However, aside from some rather equivocal clinical studies, primarily in the treatment of depression,[29,30,35,39] and another report of success in treating withdrawal from alcohol and opiate addiction,[42] no significant contemporary psychiatric studies involving cannabis therapy have been reported to date.

The Current Status of Cannabis Research

Many current "authoritative" publications unequivocally state that there is no legitimate medical use for marijuana. As compared with the 1800's, this century has seen very little medical research on the array of some 20 chemicals that are found in the hemp plant.[37]

Today's readers may tend to be skeptical about a report of a cure for gonorrhea published over a century ago.[19,25] Such findings may bear reinvestigation, however, in the light of a report from Czechoslovakia in 1960 that cannabidiolic acid, a product of the unripe hemp plant, has bacteriocidal properties.[7] Some of the therapeutic applications reported in the early medical papers have been corroborated by later investigators, but for the most part the therapeutic aspects of cannabis remain to be re-explored under modern clinical conditions.

In the past 20 years, clinical and basic research on cannabis have dwindled to practically nothing. The record of tax stamps issued by the Federal Bureau of Narcotics for cannabis research, as compared with those for research on narcotic drugs, tells the story of the 20-year "drought" in the investigation of cannabis products:[43]

	Users for Purposes of Research, Instruction, or Analysis	
Year	*Narcotic Drugs*	*Marijuana*
1938	....	5
1941	94	..
1943	....	43
1946	323	..
1948	....	87
1951	1078	..
1953	....	18
1956	284	..
1958	....	6
1961	344	..
1965	431	16

Eleven studies funded by the National Institute of Mental Health in 1967 concerning cannabis were either specialized animal experiments, part of an observational sociologic study of a number of drugs, or explorations of chemical detection methods.

The Future of Cannabis and Medicine

Unless existing restrictive state and Federal laws governing marijuana are changed, there will be no future for either modern scientific investigation or controlled clinical trial by present-day methods.

A concerted effort is indicated for full-scale investigations where knowledge is lacking. Acute and chronic effects of cannabis should be restudied by modern methods. Metabolic pathways of action and detoxification need exploration by the pharmaceutical means of today. Chronic toxicity studies must be undertaken to examine possible long-term effects of cannabis use.*

Medical science must again confront the problems of cannabis' insolubility in water and its variable strength. Since human and animal responses vary a great deal, individual doses must be titrated. The popular "double blind" type of study methods will require revision. The reporting of personal drug experience was once acceptable to the scientific community.[15,22,25,29,34,39,44] Humans who are drug "sophisticates" will again become indispensable to psychoactive drug research, as wine tasters are to the wine industry, for only humans can verbally report the subtle and complex effects of these substances.

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*Cunningham in 1893 found no gross central nervous system changes with chronic administration of hemp drugs to primates over several months.[8]

Government agencies having stimulated little significant clinical research in this field, the pharmaceutical industry should take the initiative in starting basic research and clinical studies into the purified congeners of cannabis for their chemical properties, pharmacologic qualities and therapeutic applications.

Possible Therapeutic Applications of . . Tetrahydrocannabinols and Like Products

Analgesic-hypnotic[16,18,19,23,25,27,33,45]

Appetite stimulant[18,25,27]

Antiepileptic-antispasmodic[9,18,27,33,40,45]

Prophylactic and treatment of the neuralgias, including migraine and tic douloureux[3,16,17,18,19,23,25,28,31,33,38,40,45]

Antidepressant-tranquillizer[6,16,18,19,23,25,31,33,40,45]

Anti-asthmatic[18,25,45]

Oxytoxic[25,45]

Antitussive[3,16,25,38,45]

Topical anesthetic[8]

Withdrawal agent for opiate and alcohol addiction[5,23,24,38,42,45]

Childbirth analgesic[12]

Antibiotic[7]

Discussion

Medicine, being an empiric art, has not hesitated in the past to utilize a substance first used for recreational purposes,* in the pursuit of the more noble purposes of healing, relieving pain and teaching us more of the workings of the human mind and body. The active constituents of cannabis appear to have remarkably low acute and chronic toxicity factors and might be quite useful in the management of many chronic disease conditions. More reasonable laws and regulations controlling psychoactive drug research are required to permit significant medical inquiry to begin so that we can fill the large gaps in our knowledge of cannabis.

GENERIC AND TRADE NAME OF DRUG

Diphenylhydantoin—*Dilantin*®

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A MURMUR IN THE NECK

On a routine physical examination, you discover a patient has a murmur in his neck, but no symptoms of vascular obstruction. What should you do?

"It has been my advice to take the murmur as evidence that the patient may have atherosclerotic disease which could at some time affect his cerebral circulation. I would put the man in my practice population, look after him fairly regularly, and instruct him about possible future symptoms.

"If I picked up this sign in the hospital when the patient came in for a major operation, I would feel justified in at least studying him arteriographically because of the low mortality risk with arteriograms. If he has a great deal of obstruction, and especially if I can squeeze out of him some past symptoms, I feel justified in doing a prophylactic operation prior to the one for which he was admitted.

"The other position you could take, and I wouldn't argue too strongly against, is that you do the arteriograms and be aware of what he has. In the event that he does have a stroke during or after surgery, you'll know where the lesion is; and if you get with it, chances are quite good he still would have a favorable response. But in general my approach to the asymptomatic obstruction is conservative."

—E. Stanley Crawford, M.D., Houston

Extracted from *Audio-Digest Internal Medicine*, Vol. 15, No. 19, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

CASE REPORTS

Neonatal Thyrotoxicosis—Elevated Long-Acting Thyroid Stimulator (LATS) in Mother and Infant

GERALD C. HAYS, M.D. *Fullerton*

FEWER THAN 40 cases of neonatal thyrotoxicosis have been reported in the literature although it is suspected that the frequency of occurrence is considerably greater.[1]

Six cases have been reported in which an elevated level of long-acting thyroid-stimulating hormone (LATS) was found in both the mother and the child.[2-4]

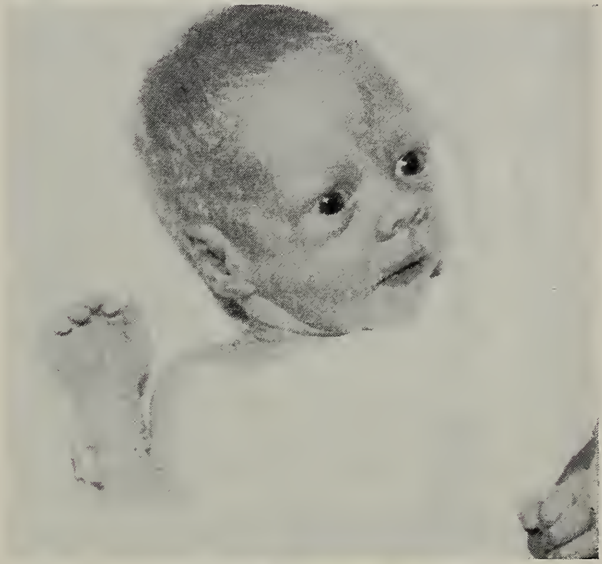
In the present case the possibility of neonatal thyrotoxicosis was initially considered because of exophthalmos in the mother.

LATS values were elevated in mother and infant.

Report of a Case

The baby, a boy, was born by breech extraction 11 September 1967 at Anaheim Memorial Hospital after 32 weeks' gestation. He was the product of the first pregnancy of an Rh positive mother. He weighed 3 pounds 13 ounces and was 17½ inches long.

The mother had had total thyroidectomy in June 1966 because of thyrotoxicosis associated with exophthalmos and goiter. Exophthalmos persisted and she regularly took desiccated thyroid, U.S.P., 0.2 gm a day. Neonatal thyrotoxicosis was first suspected after the mother's mild exophthalmos was observed by the pediatrician.



Patient at age nine days.

Noted on repeated examination of the infant were slight exophthalmos, sinus tachycardia (150 to 220), hyperactivity, diffuse goiter and poor weight gain (only 2½ ounces between age three and fourteen days despite good appetite). There was no tachypnea after age two days and no hepatomegaly at any time. Clinical evidence was observed of idiopathic respiratory distress syndrome (not radiographically confirmed) during the first two days of life.

Oral or diaper region moniliasis was noted intermittently from age nine days to two months despite nystatin therapy by ingestion and topical application. Protein-bound iodine at age two days was 19.1 mcg per 100 ml but was reported as iodine-contaminated (although there was no discoverable reason for contamination). At ten days

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Submitted 28 June 1968.

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the results of thyroxin-by-column and the triiodothyronine tests were elevated (over 14 mcg and 42.4 mcg per 100 ml. respectively). At 11 days the mother's and infant's LATS levels were high (the mother's 629 and the infant's 154, compared with the "no response" level of 100).

The baby was treated with phenobarbital, with or without Lugol's solution, from age 12 days to two months. At age two months he was thriving and weighed 10 pounds 3¼ ounces. The heart rate was 144, the thyroid gland was barely palpable and results of a T3 test and T4-by-column were within normal limits (9.3 and 3.1 mcg per 100 ml, respectively).

When the baby was seven months old the thyroid gland was not palpable, the heart rate was 132 and growth and development were consistent with his age.

Discussion

Most cases of neonatal thyrotoxicosis are mild and have an uneventful course with or without therapy.[5,6]

Occasional cases are severe enough to cause the infant to be seriously ill; and sometimes (rarely) it causes death.[5,7]

Various therapeutic measures have been suggested, including corticosteroids and antithyroid drugs prenatally, exchange transfusion, phenobarbital, iodides, antithyroid agents and anti-heart failure measures postnatally, depending upon the clinical situation.

It is difficult to know which method of management is most effective, because of the variability of severity of the disease, the lack of a large series of cases of comparable clinical severity treated in various ways in controlled studies, and the relative unavailability of LATS studies (which should be useful in predicting thyrotoxicosis in the infant if done on the mother in mid-pregnancy).

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A RESPITE FOR THE MOTHER OF A HYPERACTIVE CHILD

"I try, in dealing with hyperactive children, to be very sympathetic with the problems of the parents. Some of these children are extremely difficult to manage. . . . I consider it a necessity that the parent get a baby-sitter, preferably every day for a few hours, and suggest that often the best kind is someone like a high school girl who's available from three to five or three to six, perhaps the time of day when the mother most needs rest, time for refurbishing and a chance to cook dinner and freshen up for her husband. The high school girl should take the child out and away so the mother doesn't even see him. This kind of relief is extremely important."

—JEROME L. SCHULMAN, M.D., Chicago

Extracted from *Audio-Digest Pediatrics*, Vol. 14, No. 13, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

Medical Progress

Current Status of the Management of Patients with Endocrine-Sensitive Tumors

Part 1—Introduction and Carcinoma of the Breast

LAWRENCE G. CROWLEY, M.D., *Stanford*

THE EVIDENCE THAT the growth of a malignant neoplasm is dependent upon the activity of another distant organ first appeared in 1896 when Beatson performed oophorectomy on two women with advanced mammary carcinoma and both experienced excellent regression of their tumor.[8] This pre-dated by several decades any concepts of endocrinology. Beatson's decision to try oophorectomy was based on his observations that secretion of milk is not affected by division of the spinal or autonomic nerves, and that the removal of the ovaries of lactating cows prolongs milk production indefinitely. These observations led to the concept of one organ "holding control" over another, and separate, organ in the absence of nervous control.[8]

The past three decades have brought forth new etiologic concepts and new approaches to the therapy of neoplastic disease. Growing knowledge of the relationship of endocrine organs and their secretions to human tumors springs primarily from the initial pioneering experiments of Huggins and associates on prostatic carcinoma.[76] Their brilliant work, demonstrating the control of testicular hormones over the maintenance of the normal prostate gland and the growth of its neoplastic offspring, led to the development of three basic concepts regarding malignant tumors. First, malignant tumor cells in some populations are not always autonomous in their growth potential with their own intrinsic control mechanisms. Second, tumor cells possess, to varying degrees, the biologic characteristics of their parent normal cells. Third, some malignant cells may be sustained, stimulated and inhibited by the action of multiple hormones circulating at physiological or pharmacological levels. A corollary to this concept is the observation that the cancer cell may remain dormant for long periods and then, rather suddenly, blossom forth and grow and disseminate rapidly. It is possible that subtle changes in the hormonal environment of the host play a role in this phenomena.

Evidence has appeared clearly indicating that tumors of some obvious endocrine target organs, such as the breast and the prostate gland, may be sensitive to changes in the patient's hormonal environment. These include the breast, prostate gland, thyroid gland, uterus, and possibly ovary. More recently certain hormonal manipulations have proved to be of some benefit in the treatment of patients with tumors arising in less obvious endocrine target organs. These include the kidney and some tumors of connective tissue origin.

The two-pronged concept of hormonal sensitivity and hormone responsiveness of some human malignant lesions has been clearly established. (I shy away from the term *hormone dependency,* for it implies absolute dependence upon a specific hormone or hormonal environment, which may be true in some experimental animal tumors but has not been proved in humans.) Hormonal sensitivity is a function of the tumor cell and is probably directly related to its degree of biologic similarity to its normal ancestral cell. Hormone responsiveness—that is, alteration in the growth of neoplastic cells—is determined by the endocrine state of the host. Thus, it is the internal endocrine environment of the host, in either its natural or ex-

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ternally altered form, which physicians must study and utilize in attempting to further understand the relationship of hormones to the initiation of neoplastic disease and to effectively employ endocrine methods in the treatment of patients with tumors sensitive to hormones.

This review will attempt to deal, in a summarizing fashion, with the current status of the management of patients with endocrine-sensitive tumors, excluding lymphoma and leukemias. The theoretical background for the choice of a specific therapy, its practical application, and expected results will be stressed.

Carcinoma of the Breast

The annual incidence of carcinoma of the breast is approximately 70 per 100,000 women and the mortality rate is 24 per 100,000 women.[48] In California, cancer of the breast comprises 23 percent of all cancers occurring in females, and the overall relative five-year survival rate is 56 percent.[123] The American Cancer Society estimates that there will be approximately 6,000 new cases of breast carcinoma in the state of California in 1968.[60]

Endocrine Factors Related to Mammary Carcinogenesis

Epidemiological studies indicate that variations in the internal hormonal environment may be associated with variations in the incidence of breast cancer, namely parity, menarche and menopause. Previous oophorectomy, nulliparity and nulligravidity increase the risk of a woman developing mammary carcinoma.[40,107,119,142] A specific incidence of breast malignancy for single nulliparous females beyond the age of 35, is 30 to 60 percent greater than in married multiparous females. Differences in death rates are similar. History of not having nursed a baby and of prolonged lactation (over two years) is more common in patients with breast cancer than in controls.[100,106,167] This epidemiological data leads to the conclusion that the risk of breast cancer is somewhat less for women who have undergone the endocrinological stimulation associated with pregnancy followed by a period of normal lactation than it is for those who have not. This further suggests that a variable hormonal environment, particularly with large fluctuations in sex steroid levels associated with pregnancy and lactation, is an overall healthier environment in the sense that it affords greater protection to women from the still unknown factors causing induction of mammary carcinoma. In Moore's series, young women who had undergone oophorectomy before the onset of malignant lesions of the breast had a significantly poorer prognosis than non-castrates.[124]

This raises the question of the potential hazard of the widespread use of oral contraceptives. Gregg[61] reported cases of increased galactorrhea, nipple and areolar pigmentation, and multiple fibroadenomata in women maintained on oral contraceptives, and many patients complain of increased heaviness of the breasts. The author recently treated a young nulliparous woman in whom carcinoma of the breast developed four months after she began taking oral contraceptives. From our present state of knowledge it appears probable that a woman with a strong family history of breast carcinoma should eschew prolonged use of oral contraceptives because of the interference with normal fluctuations of sex steroid levels.

A family history of breast cancer involving mothers, and particularly sisters and daughters, is associated with an increased risk of mammary carcinoma.[4,171] However, nothing is known about the variations or similarities of the hormonal environment within families with a high incidence of carcinoma of the breast. Characterization of the endocrine environment of the woman is usually assessed by measuring the urinary excretion levels of several hormones and their metabolites. In a group of 56 premenopausal and 58 postmenopausal women the levels of excretion of androsterone and etiocholanolone were significantly lower in premenopausal women with mammary carcinoma than in matched women with benign breast disease or sick and well controls. This was not noted in postmenstruants. The ratio of 11-desoxy-17-ketosteroids to 11-oxy-17-ketosteroids was lower in premenopausal women with carcinoma.[114] Similar studies of the excretion of urinary estrogens revealed that premenopausal women with mammary carcinoma excreted a lower proportion of their total estrogens as estrone and a higher proportion as estriol. Postmenopausal women with breast cancer also excreted higher proportions as estriol.[115] Lemon and coworkers studied the excretion of the three classical estrogens and noted that the ratio of estriol to estradiol plus estrone was 1.2 to 1 for controls against 0.7 to 1 for women with breast cancer.[103] After endocrine intervention a rise of the quotient toward normal was associated with response. From animal studies reported by other investigators,[67,74,149,165,169] Lemon came to the opinion that estriol represents an impeded estrogen which inhibits the biological activity of estradiol and estrone and thus reduces their possible carcinogenicity.

However, studies utilizing administered radioestradiol produced an opposite result which indicated that postmenopausal patients with breast carcinoma excreted higher amounts of estriol and a higher quotient of estriol over estradiol plus estrone than was seen in controls. The striking finding in this study was that women with mammary carcinoma excreted smaller amounts of estradiol and the ratio of estradiol to all its metabolites was much lower than that found in normals.[23] This suggests that post-menopausal women with breast cancer have an environment relatively low in the more active estrogen, estradiol. Brown reported similar findings.[12]

In a prospective study, Bulbrook and Hayward[18] collected almost 5,000 urine specimens from women between the ages of 35 and 55 on the Isle of Guernsey. Since initiation of the study in 1960, carcinoma of the breast has developed in 19 women. The urine samples were subjected to multiple hormone assays and the results so far indicate that a majority of the women with carcinoma of the breast had abnormal excretion levels of etiocholanolone and/or 17-hydroxycorticoids. This abnormality was characterized by a subnormal amount of etiocholanolone and a lower etiocholanolone/17-hydroxycorticoid ratio.

This report tends to correlate the previous findings of these investigators, in 1962, in a retrospective study of patients with known breast carcinoma.[19] In the latter study, 17 women with breast carcinoma were compared with matched controls (five or ten controls for each carcinoma patient) and the difference from the mean of the matched group of each cancer patient was calculated. The breast cancer patients showed multi-directional differences from the normal controls but there was a clear tendency for the cancer patients to excrete subnormal amounts of etiocholanolone. The difference was magnified if the differences in 17-hydroxycorticoids and etiocholanolone were statistically compared together rather than individually. This is similar to Bulbrook and Hayward's findings in an earlier study of 36 women with breast carcinoma in which two-thirds of the patients excreted subnormal amounts of etiocholanolone.[17] The authors theoretically speculate that a low androgen environment may allow normal levels of estrogens to be unantagonized in their biological activity and thus establish an environment for prolonged estrogen stimulation with a resultant increased incidence of mammary carcinoma.

Jull and coworkers[86] failed to find any difference in the excretion of estrogens between premenopausal women with breast cancer and normals. This was a carefully conducted study with urine collection from 13 women during multiple days of the menstrual cycle. One of the problems in interpreting urinary excretion data, as will be noted on other occasions in this review, is that hormonal excretion levels vary from day to day; therefore, it is not advisable to give too much credence to the contents of a single 24-hour urine sample. Furthermore, it is known that the three classical estrogens represent only 60 to 75 percent of total estrogen excretion.[23]

In summary, more and more reports are beginning to appear which suggest that a significant percentage of women with carcinoma of the breast may have an abnormal hormonal environment as reflected by deviations from normal in their excretion of estrogens and androgens and hydroxycorticoids. However, the evidence so far is fragmentary and somewhat conflicting. As was mentioned above, urinary hormonal assays are notoriously difficult to evaluate in view of the problems of accurate urine collection, daily fluctuations and the wide variations in normal levels.

Adjuvant or Prophylactic Endocrine Therapy

Prophylactic oophorectomy or ovarian irradiation has been advocated by many workers for a number of years. This recommendation is based upon the observation that approximately 50 percent of all patients, and 65 percent of patients with positive axillary nodes at time of mastectomy, are destined to have metastatic lesions. Furthermore, small tumor deposits theoretically are easier to suppress or eradicate than larger tumor deposits, and as a corollary, numerous, as opposed to a few, tumor deposits have a greater deleterious effect on the host organism and may precipitate a general lowering of host resistance. Therefore, prophylactic treatment (before evidence appears of recurrent or metastatic disease) is aimed at suppressing or eradicating micrometastasis and it is hoped that such treatment will be more successful than the later therapeutic endocrine treatment of patients with overt or symptomatic disease, at which time the tumor deposits are either relatively large or numerous or both. Most advocates of prophylactic therapy would restrict its use to premenopausal or early menopausal patients with axillary lymph node involvement proven at mastectomy.

Prophylactic oophorectomy has been practiced for more than 30 years but very few reliable studies have been reported conclusively demonstrating any real benefit. Kennedy et al,[92,93] in a large retrospective study comparing therapeutic and prophylactic oophorectomy, demonstrated a prolongation of the free interval after castration—38 months against 21 months for the controls—but there was no significant difference in the total length of the survival from time of mastectomy.

Nissen-Meyer[134] claimed a significant increase in the survival rate and a lengthening of the free interval up to four years after prophylactic ovarian irradiation in Stage II postmenopausal patients. He noticed an increase from 57 to 65 percent of the number of patients alive without recurrence at four years and an increase in survival from 63 to 75 percent. He was so convinced of the value of this form of treatment that he did not feel he could withhold prophylactic oophorectomy for the premenopausal women with Stage II disease and, therefore, had no controls in this group. However, he did compare ovarian irradiation with surgical oophorectomy in this latter group, and both methods for obliterating ovarian hormone production yielded similar results. He was unable to detect any benefit with either method in patients who had Stage I disease with no nodal involvement.

The conclusion drawn from Nissen-Meyer's and other studies[69,70,138,147,163] is that there is no benefit from prophylactic oophorectomy in patients with Stage I disease, but there is a suggestion of some benefit for patients with Stage II disease manifested particularly by prolongation of the free interval. Proof of any further benefit is lacking. The results, however, are of sufficient interest to warrant controlled prospective clinical trials comparing survival, free interval, and other data for patients with Stage II breast cancer with and without prophylactic oophorectomy. Such a trial is being conducted under auspices of the Surgical Adjuvant Breast Project operated by the Cancer Chemotherapy National Service Center of the National Cancer Institute. However, no results are reported as yet.

Nissen-Meyer currently advocates the use of oophorectomy or irradiation therapy plus prednisone, 2.5 mg per day.[134] The latter drug is aimed at suppression of the secretions of the pituitary and adrenal cortex. In comparing patients so treated with controls from a previous series, he noted that the proportion of people alive without recurrence at five years had increased from 25 to 60 percent. However, the series was neither randomized nor performed simultaneously.

Kennedy's report[93] correlates well with the report of the Subcommittee on Breast and Genital Cancer[33] in 1960, which indicated that there was a significantly longer free interval in women whose natural menopause was interposed between a radical mastectomy and the onset of recurrence, than in women whose onset of disease and recurrence occurred all before or after cessation of menses. The reports of prophylactic castration have indicated some possible benefits and, along with the results of some of the epidemiological endocrine studies, suggest the tentative conclusion that an abnormal environment—namely, a reduction in the levels of circulating estrogens and progestins—may impede the growth of clinically unrecognized mammary carcinoma cells. This is a reasonable point of argument in view of the fact that it is well recognized that overt tumor deposits frequently regress after similar therapy.

Therapeutic Endocrine Therapy

Approximately 40 to 50 percent of women who undergo treatment for primary carcinoma of the breast are destined to have recurrence or metastatic disease or both. Cures have not been reported after the development of metastatic disease; however, various forms of endocrine treatment have induced substantial regressions of tumor deposits, often for months, and occasionally for several years.

Hormonal therapy is strictly palliative. Such therapy is designed to accomplish two purposes: first, to ameliorate the symptoms caused by the neoplastic growth; and, second, to substantially lengthen the useful life of the patient. If neither of these goals is attained, the treatment is not truly palliative. Rarely is either accomplished without the induction of true regression of tumor. In only a minority of cases are palliative efforts truly helpful to the patient, but when real palliation is obtained, it is well worth the effort. Alteration of the hormonal environment by the subtraction or addition of a specific hormone or multiple hormones has been clearly demonstrated to influence, in a favorable fashion, the growth rate of advanced and metastatic mammary carcinoma in about 30 to 40 percent of patients so treated. These observations have been consistently made since the original report by Beatson, in 1896, that two women with advanced breast carcinoma showed a remarkable remission of their tumors following oophorectomy.[8]

Endocrine therapy is divided into two subdivisions: (a) the subtraction of hormones, accomplished by ablating the ovaries, the adrenals, or the pituitary, or a combination of these done simultaneously or serially; and, (b) the addition of one or more hormones (natural or synthetic), including estrogens, androgens, progestins, corticoids and thyroxin. In the first category, specific hormonal therapy is directed toward removing the source, or sources, of the production of hormones such as estrogens, progesterone and pituitary factors which are known to be stimulatory to the breast and which may also stimulate its neoplastic offspring. In the second category, a specific endocrine treatment program is directed toward either altering the secretion or antagonizing the peripheral effects of one or more of these same hormones. Paradoxically, this may include the use of large doses of one or more breast-stimulating hormones.

For practical purposes, women are frequently divided into two groups depending upon the presence or absence of evidence of significant ovarian function. Menstruants plus early menopausal women (less than five years post-cessation of menses or showing continuing clinical and/or biochemical evidence of significant ovarian activity) are grouped together and therapy for these women is aimed, in general, at the reduction of the levels of circulating estrogens and/or progestins. This is done on the basic theory that their tumors arise and flourish in an environment rich in ovarian hormones and thus, deprivation of sex steroids is most likely to inhibit the growth of the cancer cell. Late postmenopausal women, whose tumors arise in an environment presumably relatively barren of ovarian hormones but rich in pituitary hormones, are frequently initially treated primarily with female sex hormones in large amounts.

Specific Treatment and Expected Results

Oophorectomy. A large amount of experience has been accumulated since Beatson's[8] original evidence, in 1896, indicating that oophorectomy will lead to objective evidence of significant tumor regression and symptomatic improvement in from 25 to 50 percent of patients so treated.[1,9,105] Castration remains the most reliable, most effective and least hazardous form of treatment. In 1962, Taylor[161] reported the results compiled from data obtained from 13 institutions which included 381 treated patients. Thirty of the patients had response to this treatment. The response rate was highest in women between 35 years of age and the onset of the climacteric. The rate of response decreases but may be still considerable in the postmenopausal years up to 65 or 70. Recent studies have indicated that a surprising number of postmenopausal women excrete moderate amounts of active estrogens well into the eighth decade.[115] Response lasts an average of about 12 months but in some cases persists for several years. Survival of the responders averages 31 months as compared with nine months for non-responders.[92] Up to 25 percent of patients will have ovarian metastasis and many will show cortical stroma hyperplasia.[153]

Radiation castration induced by dosages ranging from 1,200 to 1,800 rads may also effectively destroy ovarian function, as was clearly demonstrated by Diczfalusy and co-workers[37] who reported decided reduction of estrogen excretion after radiation and no further reduction after subsequent oophorectomy. However, reduction of the estrogen levels is much slower following radiation than following castration, averaging three months for maximal reduction.[131] Overall clinical results are similar in both the radiation and oophorectomy groups.[1,9]

Surgical oophorectomy is a simple procedure with an exceedingly low morbidity and mortality and it remains the preferred method, since it produces immediate hormonal changes and this timing may be important in turning the tide against a rapidly progressive metastatic tumor.

Adrenalectomy. Bilateral adrenalectomy was first utilized successfully by Huggins and Bergenstal[72] in 1951, in the treatment of patients with metastatic mammary carcinoma and they reported excellent tumor regression in four out of seven patients. The initial and current theoretical basis for ablation of the adrenal glands remains that the adrenal cortex secretes significant amounts of estrogens and progesterone, particularly after interruption of ovarian sources, therefore, removal of this secondary source of supply should reduce female sex steroid levels to zero and thus remove, as completely as possible, all such hormone stimulation of mammary tumor growth.[16,157]

A sampling of published reports which include over 2,000 cases of adrenalectomy, clearly indicates that bilateral adrenal ablation induces an objective response exceeding four to six months in duration in approximately one-third of the patients so treated.[22,27,28,30,32,47,87,120,132] The reported rates of response, which, unfortunately, are based upon dissimilar criteria, vary from 28 to 45 percent. Macdonald,[120] in a large study involving multiple centers in the United States, reported a rate of response of 28.4 percent.

The mortality rate for adrenalectomy has steadily fallen over the years, and in large centers it is currently about 5 percent. Increased surgical experience and better selection of the patients have brought about this favorable reduction. Preterminal patients should be excluded from this procedure since the mortality rate in this group approaches 100 percent. Adrenalectomy may be accomplished by an anterior laparotomy approach or by a posterior bilateral resection of the twelfth ribs. The latter method is preferred, particularly, if previous oophorectomy has already been accomplished, for the morbidity is markedly less than in the laparotomy approach.[27]

Replacement therapy is usually managed with oral cortisone, 37.5 to 50 mg a day. Some patients require an additional supplement of 0.1 mg of fluoro-hydrocortisone every other day. The patient must be clearly warned that increased corticoid intake is mandatory if unusual stress should occur, such as a febrile illness.

Responses have been noted in patients with metastatic deposits in all organ systems, including extensive hepatic involvement, except for the central nervous system. Preterminal conditions and symptomatic cerebral metastatic disease or severe respiratory insufficiency due to lymphangitic spread of tumor constitute the major contraindications to adrenalectomy.

A major point of controversy is whether adrenalectomy should be performed in combination with oophorectomy or sequentially following a trial of castration alone. The sequential approach has been generally favored.[39,144] This position is based upon several factors: (a) The mortality and morbidity is higher after the combined operation as opposed to oophorectomy alone. (b) Adrenalectomy requires perpetual corticoid replacement therapy. (c) Several studies have indicated that initial response to oophorectomy is a good indicator that response to adrenalectomy or hypophysectomy will also occur at a later point in time.[21,44,51,120,137] The rate of response to adrenalectomy, following a response to oophorectomy, averages close to 45 percent; whereas, after failure to respond to oophorectomy, it averages about 15 to 20 percent.[31,120] The response rate to adrenalectomy following either combined oophorectomy and adrenalectomy, or adrenalectomy alone, has been about the same—31 percent for adrenalectomy alone against 34 percent for a combined approach.[51] The duration of response and average survival time are about the same in both groups—12 and 21 months, respectively.[51] The author, in a series of 39 consecutive cases of adrenalectomy, in half of which the operations were done sequentially and in half combined with oophorectomy, noted that the response rate was similar in the two groups, 36 against 29 percent, but the survival time of the responders, measured from the time of the initial ablative therapy (oophorectomy), was longer in the group done sequentially, and this was particularly true if the patients responded to both oophorectomy and adrenalectomy done separately.[27] The mean survival time was 36 months in the latter group as opposed to 21 months in the combined adrenalectomy-oophorectomy responder group. (d) Utilizing the sequential approach, the oophorectomy responder may be spared the unnecessary morbidity, mortality and dependence upon cortisone replacement therapy for many months, and her eventual life-span may be lengthened by gaining two separate episodes of response.

A contrary view is held by some clinicians[20,118,132] who argue that combined ablative therapy offers three advantages. (1) A few patients who do not respond to oophorectomy may deteriorate so rapidly that later adrenalectomy cannot be accomplished. Thus, a few such patients will be denied a form of therapy which offers them a reasonable hope for a response. (2) Response and prolongation of survival is best accomplished by early, rather than late, intervention when the total tumor mass is greater and the patient's general condition is poorer. (3) Combined adrenalectomy and oophorectomy more effectively reduces sex steroid levels than oophorectomy alone.

The theories are reasonable; however, pertinent comparative studies to answer the question in any authoritative manner are lacking. The question is important, and it can and should be answered by a prospective, statistically sound study comparing the two modes of ablative therapy. At present I would favor the use of the sequential approach for all menstruants and for women in the early postmenopausal years who demonstrate either clinical or laboratory evidence of continued relatively high levels of estrogen production. This attitude is based on the evidence that double responders have a longer survival time and they may be spared the morbidity arising from the major ablation for a significant period of time. Women of all ages with very rapidly growing tumors, or postmenopausal women with atrophic vaginal smears or low levels of urinary estrogens should probably be treated by combined castration and adrenalectomy.

Hypophysectomy. Theoretically, hypophysectomy possesses a possible therapeutic advantage over adrenalectomy with, or following, oophorectomy since ablation of the hypophysis reduces not only the secretion of adrenal sex steroids which may be stimulatory to the breast and its neoplastic variant, but it also removes the secretion of prolactin and growth hormone which also may be direct mammary tissue stimulants.[53] However, several years of clinical experience indicates that pituitary ablation does not have any distinct advantage over adrenalectomy in the rate of response, the duration of response, or survival time.[120,145] Hypophysectomy may be accomplished surgically by several routes or with several radiation sources. Luft and Olivecrona,[112] in 1952, first demonstrated the dramatic regression of metastatic breast tumor deposits following hypophysectomy. The greatest experience has been gained with transcranial hypophysectomy. The report of the Joint Committee Studies comparing adrenalectomy and hypophysectomy indicated that a response rate of approximately 30 percent can be obtained, which is similar to the results with adrenalectomy.[120] However, the complication rate is somewhat higher with pituitary ablation and the hormonal replacement problem is more difficult. Complications include diabetes insipidus, which occurs in about one-fifth of the cases, anosmia, cerebral spinal fluid leak, visual field defects and incomplete hypophysectomy.[91] A transsphenoidal route has been employed but a sufficiently large number of cases have yet to be evaluated and reported to definitely establish its relative effectiveness.[172] The mortality rate varies from 2 to 10 percent.

X-ray radiation has been unacceptable due to the extremely high doses required (12,000 to 14,000 rads) to induce profound pituitary atrophy and because of the high incidence of secondary visual damage.[62] Implantation of a beta ray-emitting yttrium via a transsphenoidal route has been performed by Forrest[50] and Moseley.[127] The procedure can be performed under local anesthesia, but great technical skill is required. Moseley[127] reports a remission in 11 of 42 patients, or 25 percent, with a low overall morbidity. A proton beam generated by a cyclotron can deliver 20,000 to 30,000 rads with great precision which will destroy the pituitary, but its use is not practical due to the paucity of such facilities.[162]

Castration plus additive hormones. Some practitioners have added androgens or corticoids as an adjuvant to oophorectomy. Nissen-Meyer[134] has reported the use of prednisone, 2.5 mg a day, after therapeutic oophorectomy with the purpose of inhibiting adrenal production of sex steroid and pituitary secretion of gonadotropins and prolactin. However, he has failed to document the anticipated hormonal changes. He is now employing this form of treatment as prophylactic therapy and claims a resultant increase in the number of five-year disease-free patients over the number achieved with prophylactic oophorectomy alone. No mention is made of the complications of prolonged corticoid therapy. In general, the simultaneous employment of multiple forms of therapy is not recommended since it confuses the interpretation of the results and there is no conclusive evidence that any advantage is gained. Oophorectomy alone remains very effective and since androgens may be converted to estrogens, the use of the latter seems doubly unwise.[135]

Androgens. Testosterone, initially utilized in 1939, was the first sex steroid noted to favorably affect the growth of mammary carcinoma.[98] Testosterone proprionate, 100 mg given three times a week, remains the standard drug. However, fluoxymestrone (Halotestin®), 20 to 40 mg a day given orally, is preferable and equally effective.

Numerous other androgenic substances have been tried without any evidence of increased benefit over the two standard drugs. Recently Segaloff[151] reported the effectiveness of delta-Testololactone, a nonvirilizing androgen, but confirmatory evidence from other workers has been sparse. The mechanism of action of androgens in suppressing mammary tumor growth is obscure. As with other hormones, large doses of androgens have significant effects upon the secretion of other endocrine glands, including the pituitary, thyroid, and adrenal glands, which results in an alteration of the general hormonal internal milieu which may be important.[41]

Androgens are thought to be antiestrogenic and recent tissue studies indicate that testosterone may be accumulated in some animal and human breast tumors.[2,36,65,146] This suggests the possibility that testosterone may have a direct effect upon the tumor. Another possibility is that the androgen molecule may successfully compete with estradiol for a receptor site on tumor cells which require estradiol for their continued growth. Some patients may notice subjective improvement without any objective evidence of tumor regression. This is probably related to the anabolic and hematopoetic stimulating effects of androgens.

Androgens have serious side-effects including the various manifestations of masculinization which most women strongly dislike. Also, hypercalcemia may be induced by the drug. The various androgens are effective in both pre- and postmenopausal women, but they are clearly less effective than either ablative procedures in the former group or the use of estrogens in the latter group. The Joint Commission Studies reported a response rate for androgen therapy of 20 percent against 30 and 35 percent for adrenalectomy and estrogen therapy, respectively.[33,120]

The relatively low response rate plus their distressing side effects have tended to relegate the use of androgens to a somewhat secondary, though important, role in the management of the women with advanced mammary carcinoma. They are currently primarily utilized after either the failure of response or the cessation of response to endocrine ablative procedures in the younger woman and after a trial with estrogens in the aging woman. However, some clinics employ androgens after oophorectomy and before attempting adrenalectomy. Dao and Nemoto,[31] in a recent report, cast serious doubt on the wisdom of this particular practice. Two-hundred and fifty-one patients were divided into three groups. The first group was treated with adrenalectomy, the second group was treated with Halotestin or dihydrotestosterone, and the third group was treated with various test androgens. The remission rate in the adrenalectomy group was 45 percent, whereas the rate in both drug groups was under 20 percent. In many patients with pulmonary-pleural disease in particular, the investigators noted that there was so much deterioration of clinical condition during androgen therapy that subsequent adrenalectomy could not be offered. It is presumed that a third or more of these patients would have responded to adrenalectomy and thus, because of the preliminary androgen trial, they were, in essence, denied this beneficial therapy.

Estrogens. The trial of estrogens in mammary carcinoma followed the demonstration by Huggins[160] that diethylstilbestrol frequently induced regression of prostatic carcinoma. The first large series was reported by Haddow in 1944.[63] A sound theoretical basis for the use and effectiveness of estrogens (and progestins) in the treatment of advanced mammary carcinoma has not been definitely established. It remains a paradox that substraction of estrogens induced by castration and adrenal suppression often induces dramatic benefit to some premenopausal and early menopausal women; whereas, the addition of these same estrogens may likewise be beneficial to older women. The dosage or circulating levels of the natural or synthetic hormone may be an important factor in explaining this paradox. Estrogens, acting in concert with progestins, corticoids and pituitary factors, stimulate the acinar and ductal development of the mammary gland. The effect of estrogens is probably a dual one: (a) a direct effect on the epithelial cell supported by the recent work of Jensen that documents the presence of an estradiol receptor in the breast cells[80] and, (b) an indirect action mediated by the anterior pituitary. Estrogens depress gonadotropin production but it is highly doubtful that this is an important action since castration, which also may inhibit tumor growth, results in decidedly elevated levels of gonadotropins. The influence of estrogens on growth hormone and prolactin production is probably more important. Furth[52] demonstrated that estrogens in small doses stimulate mammatropic hormone production in rats; whereas large doses are inhibitory. Meites and co-workers[122] noted similar effects of estrogens on prolactin production in humans.

This concept of a low dosage of estrogens stimulating, and high doses inhibiting, pituitary mammatrophic factors correlate well with the observation that, with the inception of estrogen therapy, a low dosage level is sometimes associated with evidence of tumor stimulation but later, as high circulating levels are obtained, tumor regression occurs.

Another interesting speculation is the observation, in several experimental animal tumors, that estrogens inhibit the growth of the malignant cells at the same time they are stimulating the normal mammary gland.[66,146] In postmenopausal women the remaining breast frequently shows signs of stimulation as evidenced by hypertrophy, increased firmness and areolar pigmentation under the influence of estrogen therapy concomitant with tumor regression. It is postulated that this paradoxical action could result from the diversion of metabolic activity away from the production of cellular protein to the production of secretory products. Thus, under a certain hormonal stimulus, normal cell proliferation could be stimulated at the expense of the growth of the neoplastic cell population.[104]

Pharmacological doses of estrogenic substances are employed. Diethylstilbestrol, 15 mg daily, remains the standard and most useful preparation. Natural estrogens, such as estradiol valerate or estradiol benzoate, are also effective in dosages substantially above physiological ranges. Rapid increase in dosage to maximal levels (15 mg q.d. of diethylstilbestrol) is recommended to avoid the possible stimulatory stage, and treatment should be continued for at least eight weeks since objective evidence of response may be slow and undramatic in appearance.[90] The rate of objective response to estrogen averages about 35 percent. It compares favorably with androgens, with approximately a 20 percent response rate, and rivals surgical ablation in effectiveness.[33,90,94] The response rate is greatest in women of advanced age and is somewhat less for women close to menopause.[33]

Estrogens are particularly effective in patients with soft tissue and pulmonary-pleural disease and somewhat less useful in patients with osseous and visceral deposits; however, patients with extensive skeletal and hepatic involvement have developed dramatic regressions. The duration of the response averages 12 months and the survival time of responders in comparison with non-responders is more than doubled.[33] Fluid retention and breast engorgement are common side-effects; they can be controlled quite satisfactorily with diuretics. Vaginal bleeding may occur but can usually be controlled by increasing the estrogen dose. However, occasionally diagnostic curettage may be necessary. Other side-effects include areolar pigmentation, and relaxation of the pelvic floor causing some tendency towards incontinence and increased libido. However, these effects are usually well tolerated, more so than the side-effects of androgens. Hypercalcemia, in the patient with significant osseous disease, remains the most serious complication of estrogen as well as of androgen therapy. Kennedy[95] reported a 3 and 7 percent incidence with estrogens and androgens respectively. This serious complication is best controlled by the cessation of hormonal therapy and the use of large doses of cortisone. Mild degrees of spontaneous hypercalcemia may be controlled on oral phosphate therapy. Massive doses of estrogens (diethylstilbestrol, 400 to 100 mg a day) have been tried in premenopausal women with objective regression occurring in four out of nineteen patients.[89] Other extensive trials have not been carried out.

In summary, natural and synthetic estrogenic hormones, in 10 to 20 times normal physiological doses, remain very effective tools for the management of the postmenopausal woman with advanced mammary carcinoma. Such therapy is well tolerated and produces significant palliation in more than one-third of the patients.

Progestins. Various pure non-androgenic progestational compounds in large doses have been utilized in limited clinical trials.[25,58,59,75,85,99] The possible beneficial mechanism of action remains obscure, but it is theorized that it may be related to inhibition of pituitary luteinizing and gonadotropic hormone and adrenal steroid production.[96,155,156] The reported results have been inconsistent: there has been occasional evidence of good responses, but in general they have been disappointing.[25,150] Muggia and coworkers[128] reported the use of an oral agent, medroxyprogesterone acetate (Provera®). Thirty-four postmenopausal women were treated, with seven responding—a response rate of 20 percent. An additional five of the ten patients responded to combined Provera and diethylstilbestrol therapy. However, in three of the five patients the benefit could have been produced by estrogen alone. Crowley and Macdonald[26] reported a response in one of twenty-two patients treated with Delalutin® (17 hydroxyprogesterone acetate) 100 mg per week, alone, but a response in six of twenty (31 percent) postmenopausal women who were initially treated with estrogens alone without benefit and to whom Delalutin, 1,000 mg a week, was added to the basic estrogen regime.

The mechanism of action of the combination of these two hormones remains obscure. Responses have been noted only in postmenopausal women—consequently, upon tumors which arose in an estrogen-progestin deprived hormonal environment. It is postulated that a pronounced reversal of this environment might have a direct inhibitory action on tumor growth. An alternative explanation is, of course, the inhibitory effect on pituitary hormore production by these two drugs.[155,156] In rats this combination in similar doses inhibits, and sometimes extinguishes, experimental mammary tumors.[78] Further trial with this combination of hormonal agents and investigations of possible mechanisms of action seem warranted.

Corticoids. Corticoids, particularly cortisone, hydrocortisone and prednisone, have produced objective regression of advanced mammary carcinoma.[83,97,101,133,140] At a minimal dosage of 100 mg a day of cortisone or comparable doses of other corticoids, urinary hormonal studies indicate that there is a reduction in estrogen and androgen production in postmenopausal women.[102] Suppression of sex steroid production by direct inhibition of the adrenal cortex and inhibition of the pituitary is the rationale for therapy. Lemon[101] adds thyroid extract because patients with mammary carcinoma have been noted to have levels of protein-bound iodine in the low-normal or sub-normal ranges and in others myxedema has developed during cortisone treatment. However, thyroid extract alone has not proved to be of any value as an antitumor agent.[43]

Lemon[101] reported remission in 15 of 31 patients,[48] and Moore[125] reported a response of 59 of 190 patients or 31 percent. They both reported an average length of remission of approximately six months, but only half of the patients had remissions longer than six months, a duration of response which is considerably shorter than the period of remission one can expect from endocrine ablative operations. The more recent studies of Gardner[55] and Stoll[154] have yielded similar results with the use of cortisone in higher dosages—up to 300 mg a day. Symptomatic improvement of brief duration is seen in many patients without evidence of any tumor response. High doses of cortisone or its derivatives have been extremely helpful in the treatment of hypercalcemia of both the spontaneous and androgen or estrogen induced variety and also in the management of symptomatic patients with cerebral metastases.[113] The beneficial action in cases of cerebral metastasis is presumably due to the anti-inflammatory action of cortisone.

The complications of corticoid therapy are several in number and occur with great frequency. They include peptic ulcers, muscle weakness, hypertension, diabetes, edema and features typical of Cushing's syndrome. A further theoretical objection to corticoid therapy is its immunosuppressant activity. If immune factors are important in deterring the spread of the neoplastic process, cortisone should be contraindicated, since it is an immunosuppressant agent. Indeed, bizarre metastatic patterns, such as duodenal metastasis and extremely widespread metastatic involvement, have been noted at autopsy on some patients who have had prolonged corticoid therapy.[152]

In general, corticoids are capable of producing symptomatic improvement in a high proportion of cases, and objective response occurs in about 30 percent of postmenstruants. However, both subjective improvement and objective response is usually of relatively short duration. The side-effects are frequently troublesome and the therapy may tend to undermine the effectiveness of natural immune barriers. Consequently, the use of corticoid therapy should be reserved for patients in whom other endocrine and chemotherapeutic measures have failed, and for the management of the specific problems of hypercalcemia and cerebral edema due to metastatic disease — situations in which corticoids are specifically indicated.

Prediction of Response. Many years of experience with endocrine manipulation in patients with advanced mammary carcinoma clearly indicate that only approximately one-third, or at the very most one-half, of the women subjected to various forms of therapy, including major surgical operations and the use of many drugs with distressing side-effects, are destined to achieve any palliative benefit—that is, effective relief of symptoms, regression of tumor or prolongation of useful existence.

If an accurate method could be devised for the pre-selection of the potential responders, many patients would be spared unnecessary, and often meddlesome, treatment which not infrequently renders the patient more symptomatic and may hasten, rather than slow, the metastatic process and the patient's death. Many efforts have been made to discover clinical and biochemical criteria by which an accurate prediction of response could be made in advance of treatment. Unfortunately, despite these substantial efforts, we are still unable to make the desired prediction and to safely exclude patients from a trial with one or more hormonal manipulations. However, some progress has been made which perhaps points the way toward further efforts. Most of the studies reported have attempted to forecast response to ablative procedures, particularly hypophysectomy and adrenalectomy, since these are the major endocrine manipulations bearing a significant mortality and morbidity. However, there also have been some studies aimed at predicting response to additive therapy as well.

Clinical Criteria for Forecasting Response

Free Interval. In general, the clinical criteria thus far established as foretellers of response to one form of endocrine therapy, apply also to several other forms of endocrine treatment, although this is not universally true. One of the most valuable means of predicting response is by establishing the rate of progress of the tumor from Stage I (limited to the breast) to Stage III (distant metastatic disease). This progress is most commonly measured by determining the time interval between initiation of primary therapy and the onset of metastasis, often referred to as the "free interval." A more valuable interval, but one not so easily nor accurately determined, is the time between the onset of the first detectable breast lump and the appearance of metastatic lesions. If either of these intervals is brief (less than 12 months), the chance of the patient's responding to any endocrine therapy is small; whereas, if the interval exceeds 24 months, the patient has a better than average opportunity of responding to one or more endocrine manipulations.

In general, it can be stated that rapid progressive metastatic disease indicates the presence of autonomous tumors which have never been, or are no longer, sensitive to changes in the hormonal environment of the host.[5,82,111,125,141] For example, Fairgrieve[46] reported that the average free interval of adrenalectomy responders is 48 months, and of non-responders 22 months. Patients with long free intervals also tend to have longer periods of remission.

Time Lag Between Reactivation of the Disease and Initiation of Therapy. McCalister[118] noted that response to hypophysectomy was increased if the time from the onset of obvious metastatic disease to initiation of surgical ablation did not exceed six months. This observation fits the concept that while some mammary carcinomas are never sensitive and others are always sensitive to endocrine products, probably most have some sensitivity to variations in the hormonal environment originally, but as time progresses the tumor, as a result of the development of adaptive mutations of the tumor, or the loss of host resistance, or both, becomes entirely autonomous from the endocrine environment of the host. Therefore, early intervention should, theoretically, be more successful. However, proof of the practical value of this concept is lacking. Many patients have been noted to have very indolent, slow-growing tumors which exist for many years; and some of these patients do and some do not respond objectively to hormonal therapy. Since hormonal therapy has not been proved to be curative, it seems wise not to waste valuable therapy and induce distressing side-effects without benefit by treating the patient when she is asymptomatic, unless there is reasonable evidence that useful survival will be prolonged. On the other hand, therapy should not be delayed so long that deterioration of the patient makes it useless.

Histologic Features of the Tumor. Although some workers believe that well differentiated tumors are more likely to respond to endocrine manipulation, correlation of the histological type and subsequent response has not been noteworthy. Both anaplastic and differentiated tumors have regressed following various types of manipulations.[54,73,143,168,170]

Site of Metastatic Lesions. The site of metastatic disease may be helpful in predicting response. In general, the response rate is higher, if the dominant or major areas of metastatic disease involves the soft tissues (including lymph nodes), the skeleton, the pleura and lungs, in that order. Tumor deposits involving the viscera, including the peritoneal cavity and liver, are more resistant to hormonal therapy.[45,64,82,84,109,118] However, hepatic involvement, once thought to be a hopeless situation, should not foreclose trial of hormone therapy, including major ablative surgical procedures, for good response may occur even in a jaundiced patient.[26,31]

Age and Menopausal Status. Although a woman's age has not been proved to be a major factor in response to endocrine therapy, it has been noted that women below 30 tend to be less responsive to hormonal changes; whereas, most women in the eighth and ninth decades tend to have less aggressive malignant growths which respond, in a high percentage of instances, to hormonal manipulation, particularly to additive therapy with estrogens.[130] Menstrual status is of importance in choosing therapy. Oophorectomy is most beneficial before menopause; estrogen therapy in the late postmenopausal years. Adrenalectomy and hypophysectomy tend to be associated with higher response rates in premenopausal women and those women five to ten years beyond cessation of menses. However, good results in women of advanced age have been reported.[141]

Response to Previous Hormonal Therapy. It is generally agreed that a good response to oophorectomy augurs well the patient's response to subsequent adrenalectomy or hypophysectomy.[7,21,44,71,82,120,137] A nation-wide study of endocrine ablative procedures, reported by Macdonald,[120] indicated that 45 percent of oophorectomy responders gained a second objective response following adrenalectomy or hypophysectomy, whereas only 11 percent of castration failures gained similar benefit. However, Dao and Nemoto[31] reported a 20 to 25 percent response rate to adrenalectomy after castration had failed. Other investigators have reported similar findings.[92,144] Response to additive hormonal therapy likewise suggests that a response to major ablative intervention may be forthcoming, but the correlations are not as positive as with castration.[6,82,91,141,143]

It has been generally noted that a patient who responds objectively to one form of hormonal manipulation frequently will respond to a second, and often a third form of endocrine therapy. Consequently, in every instance, cessation of initial response to a given form of therapy should be followed by further attempts at hormonal manipulation. A given patient has been known to respond to as many as four or five different treatment programs. However, failure to respond to initial treatment should not deter the physician from utilizing another method. So-called rebound regression is occasionally seen after cessation of additive hormonal treatment, particularly with estrogens and androgens.[88] A significant response may occur in up to 10 percent of patients and, consequently, physicians should take advantage of this potential effect by delaying, when possible, the institution of a new therapeutic regimen. However, if the patient's disease is progressing very rapidly, this may be neither wise nor feasible.

Summary of Criteria for Forecasting Response

In summary: (a) slowly growing tumors best exemplified by a prolonged free interval (exceeding 24 months); (b) a relatively brief time lag between onset of discernible metastasis and initiation of therapy; (c) the localization of metastatic lesions in the soft tissues, bones and pulmonary-pleural areas, as opposed to visceral areas; (d) advanced age; and (e) a previous response to castration or other form of initial endocrine therapy are all favorable factors foretelling that the patient should have a better than average chance of responding to one or more endocrine manipulations, particularly the major ablative procedures. Nevertheless, significant responses may occur in occasional patients in whom only one or two or even none of these favorable signs are present.

Biochemical Factors Predicting Response

During the past two decades, numerous attempts have been made to establish measurements of biochemical factors which would accurately predict future response to hormonal therapy. In the premenopausal and early menopausal woman, the tumor arises and flourishes in an endocrine environment relatively rich in ovarian hormones. Consequently, many attempts have been made to correlate the urinary excretion patterns of the metabolites of estradiol and progesterone with subsequent response to major ablative procedures. To date, there is a noteworthy lack of any proof that such correlations exist. However, some interesting leads have developed.

The search for useful data is difficult because available chemical methods for measuring urinary estrogen levels, although superior to earlier bioassay techniques, are not entirely satisfactory, since complete hydrolysis of the estrogen conjugates is impossible to obtain and very small amounts of many of the metabolites cannot be detected.[23] Utilizing the Brown method and its modifications, Strong,[158] Brown,[11,13] Bulbrook,[14,16] Swyer,[159] and others[116,136] failed to demonstrate that response to surgical endocrine ablation can be predicted by urinary estrogen excretion levels. However, Brown and coworkers[13] reported that a combination of high estrogen excretion levels plus histological evidence of active stimulation of the opposite normal breast could be used to predict response to adrenalectomy and hypophysectomy. But, the series was small and false negatives occurred. In 1966, Lemon[103] reported a urinary quotient of estriol over estrone plus estradiol as an index of the ratio that impeded estrogens (estriol), which do not stimulate the mammary gland (and presumably mammary tumor), bear to stimulating estrogens (estradiol and estrone). Lemon claimed that two-thirds of breast cancer patients have a sub-normal quotient, indicating a high level of unimpeded active estrogens, and that a response to any type of hormonal manipulation did not occur unless the quotient rose to normal levels after therapy. Although the study included 34 cases, it failed to predict response in advance. It is important to point out that if estrogens do stimulate mammary carcinoma, relatively small amounts of the active hormone, probably estradiol, may be all that is necessary. Total estrogen production and high excretion levels are probably less important than the relative levels of circulating highly active estradiol. Relatively high levels of estradiol and low levels of estriol produce a more active estrogenic environment than the converse.

Despite the advantage of detecting small amounts of many urinary estrogen metabolites, the measurement of the excretion of the metabolites or administered radioestradiol in postmenopausal women failed to predict response to subsequent estrogen therapy.[23] In 1960, a group of British workers reported a study analyzing the urinary excretion paterns of 17-hydroxycorticoids and androgen metabolites, before adrenalectomy and hypophysectomy, in a large group of women with metastatic breast carcinoma.[15] From these data, they developed what is known as the Bulbrook-Hayward discriminant, which is calculated as follows: D = 80 = 80 (17 OCH + etio) where D = discriminant; 17 OCH = 24-hour urine excretion of 17-hydroxycorticoids in milligrams; and etio = 24-hour urinary excretion of etiocholanolone in micrograms. This discriminant becomes strongly positive when the etiocholanolone excretion level is high and the 17-hydroxycorticoid level is low. They classified their patients into three groups: (1) Women with a strongly positive discriminant; (2) women with a discriminant approximating zero; and (3) women with a strongly negative discriminant. They observed that patients with a positive discriminant were more likely to obtain objective response following adrenalectomy or hypophysectomy and, conversely, patients with negative discriminants were associated with a lack of response. Group 2 patients were distributed through both the responder and non-responder groups. These studies suggested that women excreting relatively high amounts of etiocholanolone as opposed to 17-hydroxycorticoids indicated a hormonal environment which was nourishing the tumor and consequently the patient would respond to ablative procedures that change this environment. These investigators subsequently reported further observations that a negative discriminant and subnormal excretions of 17-desoxy-17-oxy steroids, particularly etiocholanolone, is found not only in women who did not respond to major ablative endocrine procedures, but also is present in many women with early breast carcinoma.[17] This abnormality would suggest a deficit in androgen production. (It should be noted that this discriminant is positive in a vast majority of normal women, although it tends to gradually become less positive with advancing age.[19]

Although the application of this discriminant by Bulbrook and Hayward to the selection of patients apparently has correlated reasonably well with a subsequent response, false positives and false negatives do occur. The studies are open to some criticism because the timing of the urine collections may be critical and many of the studies reported were done ten days after a major operation (radical mastectomy), at which time it is known that there is a depression of androgen production and a stimulation of corticoid production. Also, it has been noted that there are large daily fluctuations in steroid excretion levels which makes interpretation of single 24-hour urine specimens difficult. However, further investigations certainly seem warranted. It is of interest that the authors have not reported a correlation of the discriminant with responsiveness to androgen therapy since their present evidence seems to suggest that the defect in androgen production is the important abnormal variation.

Correlations of 17-ketosteroid production,[3] beta-glucuronidase determinations,[19] urinary calcium excretion levels following cortisone administration,[82] stilbesterol stimulation, prolactin stimulation tests,[117] and urinary gonadotropin levels[108] have failed to demonstrate conclusively any reliable prognostic guidelines. Moore[125] recently reported a new incremental ratio discriminant which measures the increment in the excretion of 17-hydroxycorticoids and 17-ketosteroids before and after the stimulation of the adrenal cortex with ACTH, plus the free interval in months. A positive discriminant was associated with 80 percent of the responders. The study was purely retrospective and false positives and false negatives did occur.

At the moment, the Bulbrook-Hayward discriminant appears to be potentially the most rewarding biochemical determination for the prediction of response. Further investigations into the exact nature of the patient's hormonal environment by progressively refined and more accurate chemical analysis may be helpful in eventually arriving at a method whereby we may accurately predict in an individual patient her chance of response to a given form of therapy. However, it is likely that such investigations will be more rewarding if hormonal levels are determined in plasma and tissues. Twenty-four hour urine specimens, in essence, represent the inactive end products of the complex metabolic activity of the several primary active hormones. In the future, attention should be turned to the determination of circulating levels and tissue concentrations of the biologically active primary hormones. There have been several reports of the uptake of isotopically labeled hormones in tissues. Glascock and coworkers[49,57] measured the uptake of tritium-labeled hexestrol in tumor deposits in humans and noted that the uptake was greater in patients who responded to oophorectomy and adrenalectomy. Ellis and Deshpande[35,42] showed a similar selective uptake of radioactive testosterone and progesterone in both normal and neoplastic breast tissue. Crowley and Demetriou[24,34] measured the uptake of tritiated estradiol in the mammary carcinoma, adjacent normal breast and muscle tissue and noted that many breast tumors accumulated greater amounts of estradiol than normal breast and that this was correlated with absence of desmoplasia in the tumor.

Correlation of these findings with response to therapy is currently under investigation. A difficult problem, however, is the finding of a considerable variation in the uptake in different portions of the same tumor. This may be related to variations in blood supply and degrees of necrosis. It also may be related to the true biologic heterogenity of the tumor. The latter possibility is suggested by the clinical observation that, on occasion, tumor deposits in one area may regress decidedly while others may remain static and occasionally even show progressive growth at the same time, thus indicating that there may be variations in the endocrine sensitivity of different metastatic tumor deposits at the same period of time.

TABLE 1.—*Average Expected Results of Endocrine Treatment for Advanced Mammary Carcinoma*

Treatment	*Response Rate*	*Duration of Response (months)*	*Survival of Responders (months)*
(A) *Pre- and early menopausal women:*			
1. Oophorectomy	35%	15	31
2. Adrenalectomy	30%	12	24
3. Oophorectomy and adrenalectomy	30%	14	22
4. Hypophysectomy	30%	12	23
5. Androgens	20%	9	18
6. Corticoids (p̄ castration)	25%	5	9
(B) *Postmenopausal women:*			
1. Estrogens	35%	15	27
2. Estrogens and progestins	27%	15	31
3. Progestins	10%	9	20
4. Adrenalectomy	25%	12	20
5. Hypophysectomy	25%	12	20
6. Androgens	20%	9	20
7. Corticoids	30%	5	9

Further investigations of the uptake and distribution of estradiol and its metabolites in mammary tumor tissue have been stimulated by the recent demonstration, by Jensen and co-workers,[80,81] that specific estradiol receptors are present in normal breast epithelial cells and in some mammary carcinoma cells. Further investigation of the quantity of such receptors and the factors which enhance or block their activity in receiving estradiol molecules may be very rewarding.

In summary, none of the biochemical criteria currently proposed for predicting response to endocrine therapy have withstood the rigors of critical analysis and practical clinical application. However, encouraging leads have been suggested and it seems only a matter of time before progressively refined biochemical analysis may yield results which will be more helpful to both the clinician and, particularly, the patient.

Summary of Guides for Therapy

The skillful management of women with metastatic carcinoma of the breast is a continuing challenge to the physicians (surgeons, internists, radiotherapists, and generalists) to whose care they are entrusted. The timely selection of the specific therapy most likely to succeed is difficult and taxes the skill, knowledge, and ingenuity of the most experienced physician. Fortunately some guides are available, based on experience. In Table 1 there is listed the average response rate,

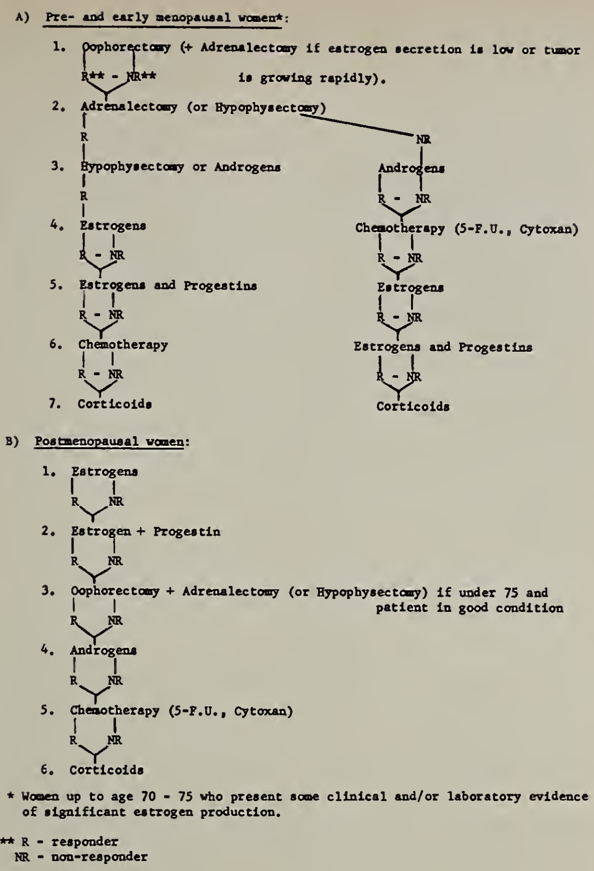
A) Pre- and early menopausal women*:
1. Oophorectomy (+ Adrenalectomy if estrogen secretion is low or tumor is growing rapidly).
R** - NR**
2. Adrenalectomy (or Hypophysectomy)
R
NR
3. Hypophysectomy or Androgens
Androgens
R
R - NR
4. Estrogens
Chemotherapy (5-F.U., Cytoxan)
R - NR
R - NR
5. Estrogens and Progestins
Estrogens
R - NR
R - NR
6. Chemotherapy
Estrogens and Progestins
R - NR
R - NR
7. Corticoids
Corticoids
B) Postmenopausal women:
1. Estrogens
R NR
2. Estrogen + Progestin
R NR
3. Oophorectomy + Adrenalectomy (or Hypophysectomy) if under 75 and patient in good condition
R NR
4. Androgens
R NR
5. Chemotherapy (5-F.U., Cytoxan)
R NR
6. Corticoids
* Women up to age 70 - 75 who present some clinical and/or laboratory evidence of significant estrogen production.
** R - responder
NR - non-responder

Chart 1.—Suggested Plan for the Serial Application of Specific Hormonal Manipulations for the Treatment of Advanced Mammary Carcinoma.

duration of response, and length of survival for the major endocrine therapies.

In Chart 1 a suggested plan is presented for the serial application of the various hormonal manipulations. In general, the ablative procedures are recommended initially for the pre- and early menopausal women followed by additive hormonal therapy and later chemotherapy, holding corticoids in reserve. In the more aged postmenopausal women, estrogens and progestins should be initially utilized. Castration and adrenalectomy or hypophysectomy may be tried up to age 75, if the patient remains in good condition. Androgens and chemotherapy should be tried in that order, holding corticoids as a last resort.

Deviations from a planned serial program often may be desirable and should be based upon important factors such as the rate of growth of the tumor, site of metastases, the emotional climate and wishes of the patient and her family, and the appearance of new modes of therapy which are scientifically sound and warrant further clinical trial. In all instances, the physician must never lose sight of the primary goal which is to induce, whenever possible, tumor regression and to provide true palliation.

Male Breast Cancer

Mammary carcinoma in the male is a relatively rare disease; the Memorial Hospital reported only 198 cases over a 41-year period.[68] The male breast resembles the pre-adolescent female breast and remains, anatomically and functionally, in a rudimentary or vestigial state. The infrequent occurrence of male breast cancer may be related to the different hormonal soil of the male. It also may be associated with the general observation that malignant neoplasms rarely occur in vestigial organs.[139] However, certain conditions are commonly thought to be associated with male carcinoma of the breast. Malignant change in the hypertrophic male breast following estrogen therapy for carcinoma of the prostate is occasionally noted, but the incidence is probably no greater than in the general population.[79,121,148] Jackson and coworkers[79] and Sandison[148] reported a high incidence of breast cancer in patients with Klinefelter's syndrome, which is characterized by gynecomastia, aspermia, testicular hypoplasia, and increased gonadotropin production. They estimated that the incidence is 66 times higher than in males who do not have that syndrome—an incidence approximating the incidence in females. The Memorial Hospital series did not reveal any association with pre-existing gynecomastia.[68]

Like females, men with breast carcinoma frequently show objective response to various forms of endocrine therapy. Excluding patients with Klinefelter's syndrome (where we may be dealing with a problem similar to carcinoma of the breast in females), therapy has been directed at removal of sources of androgens and, concomitantly, estrogens. This has been accomplished initially by orchiectomy followed by adrenalectomy or hypophysectomy or both. Treves[164] reported a subjective response in two-thirds of patients who were castrated. Several workers have reported small series of adrenalectomy with approximately a 40 percent response rate.[29,72,77,126] Luft and Olivecrona[110] reported two cases deriving excellent objective regressions after hypophysectomy. Geller reported some success after administration of Delalutin.[56] Trials with other additive hormones, including estrogens and androgens, have not yielded beneficial results, but corticoids, as noted in females, may have limited usefulness.[81] Hormonal assays of the urine, which have been so frequently employed in females, have not been correlated with castration response in males, although estrogen excretion levels in males with breast cancer have been reported to differ from that of normal men.[76] In the light of the sparse data available, it can only be stated that castration has a proved and well established place in the treatment of male patients with metastatic breast carcinoma. However, early results of both adrenalectomy and hypophysectomy are promising and certainly worthy of further trial.

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MEDICAL STAFF CONFERENCE

Coma in Myxedema

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Associate Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. HALL:* The patient is a 67-year-old Ceylonese-English woman who was admitted because of arthritis and increasing somnolence of six months' duration. In 1950 total thyroidectomy was performed in Hong Kong for an asymptomatic goiter. At that time the patient weighed 154 pounds. She noted gradual gain in weight between 1950 and 1953, at which time she weighed 208 pounds. During that same time she noted the onset of rather severe arthritis affecting the knees, shoulders and hips.

Between 1964 and 1967 she was treated by several different physicians with aspirin, indomethacin, intermittent prednisone, and intraarticular hydrocortisone. Either because of her obesity or because she appeared hypothyroid, she was treated for one week with triiodothyronine with no response, and therapy was discontinued.

In December of 1967 she was seen in our clinic because of exacerbation of arthritis. She appeared myxedematous and x-ray studies showed severe degenerative arthritis. The F_{II} test for rheumatoid factor was negative and the protein-bound iodine level was 2.1 μg per 100 ml. As she did not return to the clinic, no thyroid medication was given.

Between January and August of 1968 she was treated with high doses of indomethacin by a private physician. She rediscovered a bottle of triiodothyronine tablets which had been in her medicine cabinet for three years and took a total of 30 tablets (25 μg size) intermittently over the eight-month period before admission; her last tablet was taken one week before admission. During the two months preceding admission she noted increasing joint discomfort, and her family complained that she was falling asleep frequently.

At the time of admission to the University of California Medical Center she was extremely obese, rather slow-moving, but very pleasant. Her voice was extremely hoarse. Blood pressure was 160 mm of mercury systolic and 110 mm diastolic, pulse rate 60 per minute, respirations 10 per minute, temperature 36°C, and weight 245 pounds. Her eyes were quite prominent, her skin was dry and scaling, and she had pretibial myxedema. A thyroidectomy scar was observed in the neck, and no thyroid tissue was palpable. The chest was clear; the heart sounds were distant. Neurological examination revealed a delay in the relaxation time of the deep tendon reflexes.

Laboratory data: hematocrit 44 percent, leukocyte count and urinalysis within normal limits, serum creatinine 1.1 mg per 100 ml, uric acid and protein electrophoresis within normal limits, cholesterol 221 mg per 100 ml, total lipids 1,050 mg per 100 ml, protein bound iodine 1.5 μg per 100 ml, T3 uptake 25 percent, I^{131} uptake at 1½ hours 6 percent and at 24 hours 23 percent. Urinary 17-hydroxy, 17-ketosteroids and the metyrapone test were within normal limits, arterial pH was 7.35, arterial pO_2 was 52 mm of mercury and pCO_2 was 50 mm of mercury, and venous carbon dioxide was 37 meq per liter. Urinary gonadotropins were present at the 5 mouse unit level, although they were negative at 80 mouse units. An electrocardiogram showed low voltage of the QRS complexes. A radiograph of the chest demonstrated an enlarged heart with a questionable left pleural effusion.

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*Clifford A. Hall, M.D., Intern in Medicine.

Thyroid replacement was postponed pending the results of the initial laboratory examinations, and the patient was noted to be alert during this week. Pulmonary function tests revealed decreased lung volumes and a pronounced obstructive component. Vigorous physiotherapy was carried out and she was treated with aspirin, 900 mg 4 times a day, for the degenerative arthritis. As she kept other patients in her room awake by loud snoring at night, she was transferred to a private room.

Eight days after admission, increasing somnolence was noted. On the ninth day after admission she was found to be stuporous and unresponsive. Neurological examination was unremarkable, blood sugar was within normal limits, arterial pH was 7.25, arterial pO_2 was 32 mm and arterial pCO_2 was 95 mm of mercury, and the serum salicylate level was 20 mg per 100 ml. Both the cerebrospinal fluid pressure and protein content were within normal limits.

The patient was transferred to the Intensive Care Unit where tracheal intubation was performed and intermittent positive pressure breathing instituted. She was given 400 μg of 1-thyroxine intravenously. After intravenous administration of 3,000 ml of 0.5 normal saline solution, the serum sodium fell from 137 to 128 meq per liter. With fluid restriction to 1,500 ml per day the serum sodium returned to within normal limits. Following this therapy her mental function improved. She was continued on intravenous 1-thyroxine 50 μg per day. After five days the endotracheal tube was removed, and she appeared to be stable on nasal oxygen. Two days later she was again unresponsive; the arterial pCO_2 was greater than 100 mm of mercury and the arterial pH was 7.13. Again the endotracheal tube was placed, tracheostomy was performed, ventilation was assisted, and she improved quickly. She was maintained on 1-thyroxine 75 μg per day. Within a week of this second episode the tracheostomy site was closed. During this period the serum total lipids decreased from the initial value of 1,500 mg to 500 mg per 100 ml and the cholesterol from 221 mg to 132 mg per 100 ml. The most recent protein-bound iodine was 4.4 μg per 100 ml and the serum thyroxine level was 3.2. At present the patient is taking 100 μg of 1-thyroxine per day. Her mental status is now considerably improved from what it was at the time of admission to our hospital.

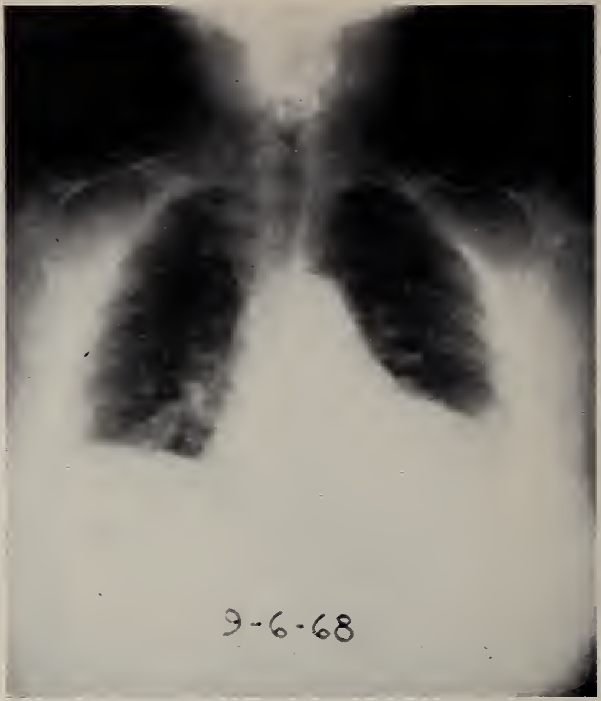

Figure 1.—Representative chest radiograph taken shortly after admission to hospital.

DR. SMITH:* May we see the x-ray films?

DR. LAWSON:† A representative chest radiograph (Figure 1) shows the heart to be somewhat prominent but with no obvious signs of pericardial effusion. There is some pleural fluid at the lung base and in addition some focal discoid atelectasis. There has been some suspicion on several films of atelectasis in the left lower lobe. Evidence of degenerative arthritis is shown on the chest radiograph, and the shoulder joints have some degenerative changes and calcifications of the soft tissues. The hand films show destruction of cartilage with spurring and osteophyte formation.

DR. SMITH: The patient is here for presentation. (Patient enters.) Thank you very much for coming. How are you feeling now?

PATIENT: I'm feeling all right, but my arthritis is starting to bother me.

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*Lloyd H. Smith, Jr., M.D., Professor and Chairman, Department of Medicine.

†Thomas L. Lawson, M.D., Research Fellow in Diagnostic Radiology.

DR. SMITH: Do you think your arthritis has improved since you entered the hospital?

PATIENT: No, it hasn't.

DR. SMITH: Have the doctors paid any attention to your arthritis?

PATIENT: They are just starting to.

DR. SMITH: You will recall that this was her chief complaint—the fact that her joints hurt. You were not concerned about feeling a little sleepy?

PATIENT: Well, I'm not sleepy now.

DR. SMITH: What changes have you noticed as to your mental awareness and wakefulness?

PATIENT: I don't fall asleep as much as I did.

DR. SMITH: How long had you had that problem of falling asleep?

PATIENT: It started about six or seven months ago.

DR. SMITH: Dr. Becker, would you like to bring out any points?

DR. BECKER:* How old were you when you first noticed the goiter in your neck?

PATIENT: I didn't notice it at all; the doctor did when I went to see him because my menstrual period was not as it should be.

DR. BECKER: You had eight children, is that right? You breast-fed all of them?

PATIENT: Yes. (Patient leaves.)

DR. SMITH: I have had the occasion to see this patient once before on that rather active morning when she lapsed into pre-coma. I can assure you that the difference today is very striking. At that time there was clearly an emergency. She had pre-coma, myxedema and hypoventilation. It is interesting to speculate on the role of this intermixture of metabolic and respiratory events in the pathogenesis of the pre-coma. It was quite clear that hypoventilation was a major part of this.

The discussion will be opened today by Dr. Charles Becker, one of our Chief Residents. Dr. Becker, who spent two years at the National Institutes of Health, where he was particularly interested in thyroid disease, will discuss the many clinical problems presented by the patient with myxedema.

DR. BECKER: Thank you, Dr. Smith. The delicate management of the acutely ill patient with severe hypothyroidism is a challenging problem for both the endocrinologist and pharmacologist. Myxedema coma is a complex subject. Limited clinical experience, uncertainty of all complicating factors, and bias in publication have made a thorough understanding of the subject difficult. To evaluate a patient with coma and myxedema requires attention to respiratory, metabolic, fluid and electrolyte, and cardiovascular problems. Even here, as you have seen, when we were alerted to the many possible problems, we had a difficult time avoiding many of the complications that are described in the literature.

The format for my discussion will be as follows: (1) brief introduction, (2) pathophysiology of the major causes of coma in severe myxedema, (3) separation of primary and secondary myxedema, (4) clinical clues to diagnosis of associated diseases which must be treated early, (5) discussion of therapy, (6) review of the patients seen at the University of California Hospital with myxedema coma during the past five years, and (7) some speculations concerning this particular patient.

Ord in 1879 was the first to describe a case of myxedema coma, but this complication was overlooked and not given major emphasis until 1953 when there was a more extensive review by Summers. I have reviewed approximately 150 cases recorded in the literature. Since not all reported patients with coma and myxedema were extensively studied with blood gas determinations and other more sophisticated procedures, it is unclear whether myxedema coma represents a distinct clinical entity or a group of multiple complications of a severe hypothyroid state. There is at least a 9:1 female to male ratio in this severe illness. It occurs in less than one percent of patients who are hypothyroid. In reviewing the cases seen in this hospital during the past five years, it was noted that there were approximately 370 patients with a diagnosis of hypothyroidism. Of these, 104 had a primary diagnosis of hypothyroidism, and yet there was only one case of documented myxedema coma. The youngest reported patient with myxedema coma in the literature was 19 years old and the oldest was 85 years old. Most of the patients are more than 40 years old. The highest incidence is clearly in the 70s, and the mean duration of hypothyroidism before the onset of coma is at least five years. Although this is generally a grad-

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*Charles E. Becker, M.D., Senior Resident in Medicine.

TABLE 1.—*Pathophysiology of Coma.*

1. Carbon dioxide retention:
    - Obesity
    - Congestive heart failure
    - Paralytic ileus
    - Immobilization
    - Infection
    - Effusions
    - Central nervous system depression
    - Aspiration
    - Large tongue
    - Weak muscles
    - Thick dry skin
2. Fluid and electrolyte disturbance:
    - Inappropriate antidiuretic hormone production
    - Antidiuresis
3. Hypothermia:
    - Not recognized frequently
    - An important prognostic sign

ual process, it can often be accelerated by associated infection, trauma, convulsions, drug therapy, surgical operation, congestive heart failure, or myocardial infarction.

At least 80 percent of the patients described in the literature had hypothermia. This is a major clue which I wish to emphasize strongly. It is often missed because the thermometer is not shaken down to a lower level. Severe hypothermia and coma should strongly suggest the diagnosis of myxedema.

Respiratory insufficiency and carbon dioxide retention, when looked for, occur in at least 60 percent of patients and is borderline in other patients. It is possible that mild stress might bring out latent respiratory insufficiency. No matter what form of therapy is used, the mortality rate in most series is at least 50 percent. This impressive mortality rate means that we must sharpen our clinical acumen and therapeutic tools to help recognize the disease process earlier and treat it more effectively.[7,8] The differential diagnosis may include brainstem infarction, hypoglycemia, uremia, respiratory insufficiency, hepatic failure, sepsis, complete heart block, or brain tumor.[2,5]

Pathophysiology

Table 1 lists the major pathophysiologic mechanisms in the coma of myxedema. There are three basic mechanisms that account for coma, but the primary one is carbon dioxide retention. There are many contributing factors in the myxedematous patient that predispose to carbon dioxide retention: Obesity; thick dry skin; congestive heart failure; ileus; immobilization; atelectasis of the lower lobes; associated infection; pericardial, ascitic, and pleural effusions; and central nervous system depression with drugs may all contribute to carbon dioxide retention. In the myxedematous patient with a large tongue, aspiration of stomach contents may lead to lower lobe pneumonia and death. The fact that this patient was snoring was perhaps a clue. What better example of upper respiratory obstruction is needed? Weak respiratory muscles due to severe hypothyroidism are probably the major factor limiting respiratory reserve.[10,11,13]

Fluid and electrolyte problems are obviously important. Inappropriate secretion of antidiuretic hormone as well as the antidiuresis phenomenon have been described in myxedema.[3] Hypothermia is a clue in diagnosis, and myxedema must always be considered in the differential diagnosis of hypothermia; I would like to emphasize again that it is an important prognostic sign—the lower the temperature, the worse the prognosis.

TABLE 2.—*Differentiation of Primary and Secondary Myxedema.*

Primary (thyroid)	*Secondary (pituitary)*
Statistically more common	Statistically less common
Previous thyroid operation	No previous thyroid operation
Obese	Less obese
Goiter present	No goiter present
Hypothermia more common	Hypothermia less common
Increased serum chloesterol	Normal serum cholesterol
Blood pressure normal or increased	Blood pressure low
Thyroid antibodies present	Thyroid antibodies absent
Voice coarse	Voice less coarse
Blood sugar normal	Blood sugar normal or low
Pubic hair present	Pubic hair absent
Sella turcica normal	Sella turcica may be increased in size
Plasma cortisol level normal	Plasma cortisol level decreased
Skin dry and coarse	Skin fine and soft
Heart increased in size	Heart usually small
Normal menses and lactation	Traumatic delivery, no lactation. Amenorrhea
No response to TSH	Good response to TSH
Good response to L-thyroxine without steroids	Poor response to L-thyroxine without steroids
PBI < 2 μg per 100 ml	PBI usually > 2 μg per 100 ml
Serum TSH increased	Serum TSH decreased

Differentiation of Primary and Secondary Hypothyroidism

Table 2 lists the important points which distinguish primary (thyroidal) from secondary (pituitary) myxedema. In the acutely ill patient this differentiation may be difficult, and corticosteroids may be a necessary adjunct to therapy. There are important clues that do give useful clinical information. Statistically, primary hypothyroidism is much more common. Previous operation on the thyroid gland obviously suggests that the defect is in the thyroid. Patients with primary myxedema are generally more obese and goiter is usually present. Hypothermia is much more common in primary myxedema. The blood pressure is frequently elevated in primary myxedema whereas the blood pressure in the patient with a deficiency of adrenocortical function is usually low. Thyroid antibodies also may be elevated in primary myxedema, and this may be a helpful clue in diagnosis. The voice is often coarser in primary than in secondary hypothyroidism. The blood sugar is generally normal in primary hypothyroidism but may be diminished in pituitary hypothyroidism. Pubic hair is said to be present in primary myxedema and absent in secondary. Normal secretion of gonadotropins, ACTH, and growth hormone is present in primary myxedema. Plasma cortisol levels are normal in primary myxedema. The heart is frequently enlarged in primary myxedema but may be small in secondary myxedema.

TABLE 3.—*Clues in the Diagnosis of Myxedema Coma.*

Clinical clues:
- Bradycardia
- Hypothermia
- Gradual increase in coma
- Winter months
- Neck scar or previous treatment with I^{131}
- Elderly women with yellow skin
  - hoarse voice
  - dry skin
  - large tongue
  - obesity
  - scanty scalp hair
  - puffy eyes
  - recent stress
  - intestinal obstruction or impaction
  - delayed deep tendon reflexes

Laboratory clues:
- EKG—low voltage, sinus bradycardia
- lactescent serum
- increase in cerebrospinal fluid protein
- increase in serum carotene level
- effusions with high protein content
- increased serum protein bound iodine in thyroiditis
- decreased serum thyroxine level and decreased T_3 uptake
- decreased I^{131} uptake

As I tried to elicit, normal menses and lactation were present in the patient presented today—she breast-fed eight children. A history of traumatic delivery, failure of lactation, and amenorrhea without hot flashes suggests secondary myxedema. One often finds that there is no response to thyroid-stimulating hormone when it is given to patients who have a primary thyroid defect. Patients who are treated with 1-thyroxine without steroids do well if the defect is only thyroidal. The tongue is said to be larger in primary myxedema. The serum protein-bound iodine is generally lower when the defect is primary hypothyroidism, and the level of thyroid-stimulating hormone as measured by the immunoassay technique is elevated.

I present these features as a rough guide to this differentiation. There are, of course, many exceptions to each point which often make this differentiation a difficult one.

Clinical Clues in Diagnosis

Table 3 lists some clinical clues which are important in the diagnosis of severe myxedema. Bradycardia and hypothermia are important clues which are often overlooked but suggest the diagnosis of increased intracranial pressure in these patients. In a patient with myxedema coma and normal body temperature underlying infection must be suspected.

The cold weather during the winter months is an important precipitating event, particularly in certain parts of the country. Of course California weather makes this less important here. In a patient with suggestive symptoms who has a neck scar or a history of I^{131} therapy, one should strongly suspect a diagnosis of myxedema. In the obese elderly patient with gradually increasing coma in the winter months who has dry yellow skin, a hoarse voice, large tongue, scant pubic hair, puffy eyes, and delayed reflexes, the diagnosis of myxedema should not be difficult. Patients may be admitted for the work-up of hypothyroidism only to lapse into coma while in the hospital, and I think this is certainly at least part of the problem in the case of the patient presented today.

There are several laboratory clues which can be of help. The electrocardiogram frequently has low voltage with sinus bradycardia. There is an increase in the QT interval. The serum may be lactescent; there may be increased cerebrospinal fluid protein without cells. There may also be an increased serum carotene level. Patients with

TABLE 4.—*Associated Illnesses in Myxedema.*

- Hypoglycemia
- Respiratory acidosis
- Inappropriate antidiuretic hormone production
- Congestive heart failure and/or pulmonary emboli
- Pleural and pericardial effusions
- Paralytic ileus
- Anemia
- Adrenal insufficiency
- Drug therapy (phenothiazines, narcotics)
- Bleeding tendency
- Seizures
- Aspiration
- Hypocalcemia (post thyroid operation)
- Hypercalcemia

myxedema may have effusions with high protein content and negative report on cell block cytology. One interesting patient with myxedema had a serum protein-bound iodine level of 4.25 µg per 100 ml. This was related not to serum thyroxine but to serum iodoproteins which were demonstrated later.[5] The classic laboratory clue is the combination of a low true thyroxine level and a low T_3 resin uptake.

Associated Illnesses

Table 4 lists the associated illness which should be treated vigorously in the critically ill patient. This represents one of the major points of emphasis in this entire discussion—that myxedema coma is an extraordinarily complicated illness. Hypoglycemia may be the cause of the coma, and it was looked for in this patient. Respiratory acidosis is a major factor to identify and treat. Inappropriate antidiuretic hormone production is equally important. The patient presented today did not excrete a water load normally. Even with the patient under observation and the house staff extremely careful, transient hyponatremia did develop. Congestive heart failure and pulmonary emboli in patients at bed rest are important complications. Pleural and pericardial effusions are complicating features common in myxedema; they must be looked for and treated if they are life-threatening.

Paralytic ileus may occur. It is interesting that a previous patient at this hospital was admitted to the surgical service because of acute abdominal pain secondary to ileus. It was not until a medical consultant noted that serum sodium was 115 mEq per liter that the diagnosis of myxedema was made. Adrenal insufficiency may complicate the clinical picture, and it is difficult to make this diagnosis in the acutely ill patient. Plasma cortisol determinations may be done rapidly and should be obtained in acutely ill patients. Narcotics and phenothiazine drugs given to the patient with myxedema may precipitate coma. The metabolism of most drugs is greatly delayed in the patient with myxedema such that their administration to a patient with severe myxedema may be dangerous undertaking.

Orr described a bleeding tendency in patients with myxedema. Diminished platelet count and increased capillary fragility may occur.[12] Seizures were the presenting symptoms in approximately 25 percent of the cases. Aspiration of stomach contents, leading to lower lobe pneumonia, may complicate the entire respiratory problem. Patients with severe myxedema may have either hypocalcemia or hypercalcemia. After operation on the thyroid gland the parathyroid glands may be transiently or permanently damaged, hypocalcemia resulting. Hypercalcemia in patients with myxedema was described by Lowe[9] and has been attributed to decreased bone deposition of calcium.

Therapy

The treatment of myxedema coma is difficult, complex, and for the most part poorly understood. The condition must be treated as a medical emergency. It must be recognized that these patients are extraordinarily labile and that complex complications develop which require treatment in an intensive care unit. The outcome in the case presented today is directly related to the excellent care the patient received in the intensive care unit. Associated illnesses must be carefully excluded, and the immediate treatment of infection is of utmost importance. One must think of the diagnosis, obtain laboratory confirmation, and treat as early as possible.

Dowling's group in Seattle suggests that intravenous 1-thyroxine is the most rational therapy.[6] Thyroxine is the major hormone elaborated by the thyroid. It is firmly bound to carrier proteins, which makes the serum protein-bound iodine a useful test in evaluating drug effectiveness. The duration of action of 1-thyroxine is longer, the onset of action is more gradual, and most importantly the drug is readily available.[4] The rationale for this therapy is based on the fact that patients with myxedema are deficient in thyroxine. Calculations based on the estimated depletion in the extrathyroidal hormone pool and the diminished fractional turnover rate suggest that the deficiency can be corrected with an intravenous dose of 500 µg of 1-thyroxine. Once the entire thyroxine deficiency is corrected, 50μg doses of oral 1-thyroxine will gradually restore the euthyroid state. Successful treatment of seven cases of myxedema coma with intravenous 1-thyroxine has been reported.[6]

There are several reports of success with triiodothyronine therapy. The report by Catz indicates that both oral and intravenous triiodothyronine therapy is useful. Catz expressed belief that triiodothyronine is the treatment of choice, as the recommended doses are small, the agent is rapid-acting, and it has a much shorter half time.[1] On the other hand, in reports emphasizing the complications of thyroid therapy in thyroid-deficient patients, triiodothyronine has been associated with arrhythmias and other problems.[14] Dr. Greenspan* felt that we could best manage the patient whose case we are reviewing today with 1-thyroxine. Regardless of the drug used initially, I feel the best choice of therapy for long term treatment is 1-thyroxine. The patient we saw today was at risk of severe hypothyroidism because she was taking triiodothyronine intermittently. With 1-thyroxine hypothyroidism develops more slowly once therapy is discontinued.

Because of the difficulty in excluding a diagnosis of adrenal insufficiency in the acutely ill patient with myxedema, it may be necessary to use corticosteroids. Since the half-time of disappearance of corticosteroids is greatly prolonged in patients with myxedema coma, doses do not have to be very high.

Certain problems in therapy deserve particular emphasis. Sedation in any form should be avoided, since this may precipitate coma. Because of a decreased insensible fluid loss, overhydration may lead to hyponatremia. Intramuscular and oral medications are irregularly absorbed, and oral therapy may lead to aspiration. Intramuscular medications definitely are not wise when circulation is compromised.

There is much disagreement about whether the hypothermic patient should be warmed. Most physicians agree that raising the patient's temperature may be dangerous because of the increased metabolic needs. These patients are poikilothermic and will respond usually to the ambient temperature. Rapid replacement of intravenous triiodothyronine may lead to arrythmias and angina. Patients with myxedema may be extraordinarily sensitive to digitalis preparations.

Review of Patients at U.C. Medical Center

Since 1963 there have been 366 cases of hypothyroidism on record at this hospital. Of these, 104 had a primary diagnosis of hypothyroidism. The only other patient with myxedema and coma was admitted to the surgical service in 1965. She was a 76-year-old woman who was thought to have intestinal obstruction. There were several notes in the chart which attempted to explain the serum sodium of 115 mEq per liter. Finally an alert medical resident made the diagnosis of myxedema. She was treated with intravenous triiodothyronine, 25 μg every six hours. She did well but complications developed, including a urinary tract infection, respiratory acidosis, and unusual anemia, and chronic lung disease. This patient died in 1967. The death certificate listed the cause of death as chronic lung disease. She did not die of myxedema coma so far as we know. Her unusual anemia was evaluated by Dr. Cline*, who found peculiar lipid laden histiocytes which disappeared after thyroid therapy. These histiocytes were quite similar morphologically to the cells seen in the bone marrow of patients with Gaucher's disease. This apparently was unique to this patient, as it has not been reported before in severe myxedema.

Some Speculations

I would like to conclude by emphasizing some specific points about this patient and by offering some speculations. The patient presented today had a normal serum cholesterol level, an anomaly which perplexed us quite a bit. Patients with severe myxedema may have malabsorption and poor dietary intake, which could explain the relatively low serum cholesterol. The T_3 resin uptake in this patient was 25 percent, which is at the lower limit of normal. The T_3 resin uptake is not affected by respiratory acidosis but is affected by aspirin. Although aspirin may have contributed to this patient's problem, it could also have increased her respiratory drive. Wolff showed that in patients with myxedema aspirin therapy may increase oxygen consumption, increase carbon dioxide production, and uncouple oxidative phosphorylation. Aspirin also displaces thyroxine from thyroxine-binding protein and increases the basal metabolic rate.[15,16] Aspirin could certainly have been a contributing factor in this patient's coma. Although she was receiving a small dose, a high blood salicylate level was found.

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*Francis S. Greenspan, M.D., Clinical Professor of Medicine.

*Martin J. Cline, M.D., Associate Professor of Medicine.

Although we thought the patient had total thyroidectomy in 1950, when the surgeons did a tracheostomy they found thyroid tissue overlying the trachea. This patient's 24-hour I^{131} uptake was 23 percent despite clinical evidence of severe myxedema. At 1½ hours the uptake was 6 percent, at 8 hours 11 percent, and at 24 hours 23 percent. Despite this uptake of I^{131} the thyroid gland was not making active thyroid hormone. The reason for this is not clear. It is possible that an abnormal iodoprotein was being made, but the protein-bound iodine level would be higher in that circumstance. Could she have been iodine-deficient? She seems to have been on a diet adequate in iodine. The possibility of an enzymatic block in thyroid hormone synthesis is raised by these findings. Certainly her thyroid gland is taking up iodine and is able to trap it, but thyroxine is not being made. This interesting problem must remain unexplained at this time.

In summary, I do not think this patient had "myxedema coma." She had severe hypothyroidism, pronounced obesity, and hypoventilation. Having had the opportunity to follow this patient's course I can conclude that coma in a myxedematous patient is extraordinarily complex, requiring constant care and early diagnosis if we hope to improve survival in this lethal but clearly treatable medical disease.

Dr. Smith: Dr. Becker has given us an excellent presentation of this patient and of the problem in general. Dr. Greenspan saw her throughout her hospital course.

Dr. Greenspan: I think Dr. Becker has raised a very interesting question: Is there really such an entity as myxedema coma? It is of great interest that as one measures the metabolic effects of the withdrawal of thyroid hormone, the brain, spleen and testes are the three organs which do not change their oxygen consumption; they seem to be able to function metabolically to some extent without thyroxine. It may be that what is called myxedema coma is really a combination of diseases, certainly exacerbated by myxedema, but perhaps not directly attributable to the absence of the hormone.

I think Dr. Becker's remarks about the role of the respiratory insufficiency and fluid and water balance are very pertinent. The incidence of hypothyroidism after radio-iodine therapy is roughly 50 percent at this time. In the future we are going to see more patients of this type who have been treated for hyperthyroidism with radio-iodine, who have no scars on their neck, and who are tired of taking their thyroid pills. I think the recognition of this syndrome will be increasingly important.

Dr. Smith: Would you agree that if the drugs are available, you would prefer 1-thyroxine to triiodothyronine? When we were faced with the immediacy of making a decision on rounds, the decision was helped by the availability of 1-thyroxine for intravenous use.

Dr. Greenspan: Both work, but I think there has been a tendency in the past to give excessive doses of triiodothyronine, which may precipitate cardiac arrhythmias or myocardial infarction. The major problem here is that one has to overcome not only the thyroid deficiency but also to correct the other diseases. Thus the replacement therapy for thyroid deficiency may be of secondary importance. Either triiodothyronine or 1-thyroxine can be used and both must be administered parenterally. The regimen used for this patient—namely a loading dose of 1-thyroxine followed by small maintenance doses daily as suggested by Holvey[6]—has been very successful and seems to avoid the problem of toxicity.

Dr. Smith: I would like to ask Dr. Fishman if he agrees that thyroid hormone is unimportant for metabolic activity of the brain.

Dr. Fishman:* Not really. First, I too would raise the question of what we should call this case. I prefer to consider it myxedema with coma due to pulmonary insufficiency. I would avoid the term *myxedema coma* in such a patient because of the suddenness of its onset and the rapidity of its clearance with respiratory management, in addition to the fact that the spinal fluid protein was normal. The effects of thyroid metabolism on the brain are complex, and most attention has been paid to the newborn because of cretinism. About two-thirds of the adult patients with clinical myxedema will have elevation of spinal fluid protein, perhaps to as high as 300 mg per 100 ml. It is my impression that the severity of the central nervous system manifestations of myxedema is correlated with high content of protein in the cerebrospinal fluid. In today's patient the protein content was quite normal. There is also a generalized slowing of electroencephalogram frequency in this condition, which provides a way to measure the response to therapy. Last, there are metabolic effects of thyroid hormone in the brain, and we have studied these effects in rats. Just as there is an accumulation of mucopolysaccharides in connective tissue systemically, one can show that in myxedematous rats there is an actual increase in the solid content of the brain—that is, a decrease in water content which is probably accounted for by the accumulation in the brain of sulfated mucopolysaccharides. So I think the relationship of thyroid hormone to brain function is complex and not just incidental.

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*Robert A. Fishman, M.D., Professor of Neurology.

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MONITORING MUSCLE RELAXANTS

"To minimize overdosage with muscle relaxants during surgery, I recommend that the course of the neuromuscular block be monitored with a nerve stimulator, and that the stimulator also be used at the end of anesthesia to monitor the reversal of curare's action with an anticholinesterase. Only the nerve stimulator will show us how profound the block is, when more drug is needed, and when the drug should be stopped. The stimulator will tell, moreover, when reversal of the block with neostigmine is complete, thus minimizing the possibility of sending a patient back to the ward with inadequate respiratory function."

—Rudolph H. DeJong, M.D., Seattle

Extracted from *Audio-Digest Anesthesiology*, Vol. 10, No. 18, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

In the Forefront

The Scientific Board

EDWARD B. SHAW, M.D., *San Francisco*

THE CALIFORNIA MEDICAL ASSOCIATION (CMA) for many years has been primarily devoted to the furtherance of scientific medicine and the promotion of patient care. However, immediately following World War II many economic factors incident to organized medicine: legislation, increasing number of third-party payments, changing fees, etc., were imposed upon it. The CMA attained a position of strength in socio-economic affairs, but, in the eyes of its members and the public, scientific interests had become weakened and fragmented. The Council, therefore, decided that this was undesirable and set about to rectify it.

Dwight L. Wilbur was chosen, along with a "blue ribbon" committee, to study this matter and recommend appropriate action. This committee proposed the formation of a Scientific Board to be charged with the responsibility of restoring the scientific and educational stature of the Association and drawing together the medical scientific organizations in California in mutual cooperation to lessen the fragmentation of the profession brought about by the growth of the specialty societies. By drawing together the scientific and educational activities of CMA and the special medical groups, interest would thus be stimulated in the CMA and serve as a factor in unification of the profession and CMA's stature as a scientific organization would be restored in the mind of the public.

The Council and the House of Delegates accepted this recommendation in 1961 and established the ground rules for this board. Membership was established at thirty-nine—18 to represent scientific sections of the CMA; 18 members-at-large to represent specialty groups apart from CMA; two to represent the Council, and the Editor of CALIFORNIA MEDICINE as an ex-officio member. All were to be members of the CMA. Each scientific section was permitted three nominations; the same privilege was given to a large number of professional societies, including the Association of American Medical Colleges. The initial selection was made from these nominations by an ad hoc committee appointed by the chairman of the Council. The length of initial terms was staggered so that there would be 12 new appointments every year, the normal term of membership being three years, with eligibility for re-election. One-half of the members of the Scientific Board were to serve as members of the House of Delegates, bringing new representation from the Scientific Assembly to CMA's governing body. The chairman of the Scientific Board was to serve as an ex-officio member of the Council. The delegates and the councilor from the Scientific Board have served, without vote, since then.

After the organization of the board, it became the responsibility of its members to elect an Executive Committee, a Committee on Nominations, and a representative to the Council. The Executive Committee was to function at the call of the chairman or any three members of the committee for any action necessary between regular meetings. The Nominating Committee, consisting of three members was to be nominated by the chairman of the Scientific Board and elected by the Board, receive and consider nominations for membership on the Board, recommend names for consideration by the Council of CMA which had final authority for appointment to Board membership. This committee also would nominate members of the Executive Committee and the members of other committees of the Scientific Board.

During the first year or two there was some organizational wheel-spinning, in an attempt to define precise functions for the board, to develop the working committees of the board, and to implement all of the activities effectively. These committees and their chairmen, without exception, have been men who were devoted and unsparing in their efforts and responsible for most of the important contributions of the Scientific Board. Efforts were directed toward improving and coordinating the undergraduate and postgraduate education of the physicians of the State and information and education of the public on health matters. It is difficult to place these several committees in order of importance in carrying out their tasks.

(1) At the time the Scientific Board was organized, CALIFORNIA MEDICINE, under the editorship of Dr. Wilbur, had become a most significant medical journal. Under his guidance it had improved steadily; his ambition was to make it the Pacific Coast counterpart of such journals as the *New England Journal of Medicine.* A Committee of the Board was established to act as advisors to the Editor, and improvement in content and quality has continued. With the election of Dr. Wilbur to the Presidency of the American Medical Association in 1968, Malcolm S. M. Watts was appointed as Editor, and Lloyd H. Smith, Jr., Associate Editor. The journal promises to be an increasingly important scientific publication.

(2) Postgraduate education has always been a thorny problem here as elsewhere. Studies of the Wilbur Committee revealed the need for coordination of efforts of the many groups providing continuing medical education — particularly with California medical schools, and for the analysis of data on the needs of physicians in this area and methods to ensure participation.

The Academy of General Practice has made continuous postgraduate education obligatory on the part of members but generally attendance has been desultory and limited to a small number, among whom are many who attend repeatedly. Data were not available on the numbers and characteristics of those members who participated or the possible contributions of continuing education to the quality of medical care.

The first chairman of the Committee on Continuing Medical Education was George C. Griffith, whose interest in this subject antedated his election to the Scientific Board by many years. This Committee was responsible for bringing some order out of the chaotic programming, and ascertaining the needs of the membership in this important field. *Coordination conferences,* which were held in November, 1964, under Dr. Griffith's leadership ultimately resulted in the establishment of *What Goes On,* a widely distributed periodic catalogue of continuing medical education opportunities and related coordination and clearinghouse service activities.

Dr. Griffith was succeeded by Donald W. Petit, whose efforts have been equally devoted and effective. Under his leadership, a Survey of Needs of Physicians in California was made and a three-year Census of Continuing Medical Education, first of its kind in the United States, is being conducted—both in cooperation with California Medical Education and Research Foundation (CMERF).

A Planning and Goals Conference in Continuing Medical Education was held in March, 1967. More than a hundred physician leaders took part, including several hospital chiefs of staff, directors of medical education, deans and associate deans of all California medical schools, representatives of specialty societies and of voluntary health agencies.

Future objectives of continuing medical education in California were considered, including (a) the role of the community hospital, (b) evaluation, (c) motivation, and (d) accreditation. In cooperation with CMA's Medical Staff Survey Committee and CMERF, all these salients are being strengthened. A new Committee on Accreditation of Continuing Medical Education has now been established under the leadership of C. John Tupper, whose work will complement the accreditation activities of the AMA.

Final reports of the Planning and Goals Conference are being used by the AMA, by many medical schools and by almost every state medical association in the United States as a guide for formulating their own activities. A second conference is scheduled for February, 1969, which will focus on problems of recertification and the development of objectives for Regional Medical Programs appropriate for CMA.

The Committee implemented the distribution of funds received by CMERF from Audio Digest Foundation to an amount of $5,000 to each of the departments of continuing education of the California medical schools last year, carrying out one of the original proposals of the Wilbur Committee. This Committee has increased statewide interest in continuing education of physicians and has established CMA as a nationally-recognized leader in this area. This is indubitably one of the most important achievements of the Scientific Board.

(3) The Committee on Scientific Assemblies was assigned the task of improving the scientific quality of Section Meetings at the Annual Session of the California Medical Association. It has long been recognized that the growth of specialty societies and the frequent meetings of all of these special interest organizations has resulted in an erosion of quality of the Annual Sessions and diminished attendance. Both the Council and the Board recognize the great importance of building scientific excellence and contributions to physician education in these annual meetings. For three years, Victor Richards and his committee struggled most effectively with this matter, and both the quality of presentations and the quantity of attendance attest this improvement.

Each specialty society has been induced to contribute its efforts to the enrichment of sections and general programs. Several of them have taken the responsibility individually for the scientific content of single sessions of the Annual Session and have made similar commitments for the future.

Under the leadership of John B. Dillon, who succeeded Dr. Richards as chairman of the Committee on Scientific Assemblies, advisory panels of medical educators and specialty society representatives have been established for several of the Scientific Sections. The work of these panels has been so effective that plans now call for extension of this concept to all sections. Activities of the sections have been broadened thereby to include not only better annual session programming but greater cooperative efforts for various medical problems. An excellent example is the current effort of the Pediatrics Section and its advisory panel, with the cooperation of the Committee on Maternal and Child Care, to study and, it is hoped, to decrease infant mortality in California.

For many years, much of the energy expended at the annual meetings had to do with the political and economic developments, which admittedly were of great importance to the profession. The present deep concern for improvement in the art and science of medicine has improved immeasurably the significance of the CMA in the minds of its members and has almost certainly improved its public image.

The Council proposed initially to have a Subcommittee on Scientific Information which would serve as a source for public education and for distribution of material through the press. The subcommittee advised on a number of matters, such as immunization procedures and the problems of cigarette smoking, but it was decided eventually that the entire Board should be responsible for public information distributed through the press and other mass media. Ad hoc committees are appointed readily for specific subjects. Their decisions are then approved by the Board and submitted to the Council.

A Department of Health Information originates in CMA headquarters, now under the direction of Harold Kay. This is responsible for *Health Tips,* which goes out to many newspapers, other periodicals, and schools. Although this is not directly under the Scientific Board, many members of the Board have contributed to these informative releases.

Some other committees of the Board are continuations of those previously developed in CMA. The Committee on Maternal and Child Care has a membership of nine, and two of the members—one in obstetrics and one in pediatrics—are selected by the Board and the Council from the membership of the Scientific Board. This Committee has functioned most usefully under the present leadership of Keith P. Russell and contributes to professional and lay education in this special area. One of its most useful functions has been to review maternal deaths and to submit a confidential report to the physician and institution involved. This Committee has developed a series of nine *Health Tips* articles on pregnancy and prenatal care which are being widely used in California schools. This work is extremely arduous and time-consuming and deserves great approbation.

The Committee on Cancer, formerly the Commission on Cancer, has continued its excellent work in its important field, especially in the matter of collecting data regarding diagnosis, therapy, survival rates, and the like. David A. Wood, now and for many years past, has had a position of great responsibility in developing this survey. This committee has played an important part in the fight for the cancer anti-quackery law, especially in the effort to have this law extended.

The Committee on Drugs and the Committee on Adverse Drug Reactions have faithfully continued work which antedated the formation of the Scientific Board.

There is no thought that the Scientific Board has reached the full height of its usefulness, and there can be no doubt of the importance of its objectives. Most of its members have been devoted to the significance of this effort and have been most faithful and unsparing of time and energy. The initial chairman, Edward B. Shaw, was succeeded by William P. Longmire, Jr., who successfully implemented many of the plans developed early. The present chairman, C. John Tupper, has assumed his task during the past year with such interest and enthusiasm that there is every reason to believe that the immediate future of the Board will be even more productive than its past performance.

PRECAUTIONS AGAINST URETERAL DIVISION

"Ureteral division can be avoided in a high percentage of cases if the following are present: a preoperative awareness of the possibility on the part of the surgeon, with urological consultation and preoperative x-ray evaluation of the upper tract; placement of ureteral catheters at the time of operation; adequate exposure and identification of the ureters and their course, which may be very devious, depending on the pathologic changes present; an in-dwelling Foley catheter in the bladder with a wide tube for bladder distention when it is necessary to definitely outline its limits (this will aid in tracing the ureter along its distal course); and the addition of sufficient indigo carmine in the bladder to quickly identify any tear, which can then be easily and effectively repaired."

—William R. Smart, M.D., San Francisco

Extracted from *Audio-Digest Surgery,* Vol. 15, No. 20, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

Medical Schools of California

Stanford University School of Medicine

TODAY, STANFORD UNIVERSITY School of Medicine, a direct descendant of the oldest medical school in the State of California, is one of the nation's most highly regarded. It has as its anlage the Medical Department of the University of the Pacific,* chartered in 1858 as the Far West's first medical school. In the top story of Dr. Elias Samuel Cooper's office near Mission and Third Streets in San Francisco, instruction began in 1859. By 1864 there were 22 students and 29 had graduated in the preceding five years. The starting of another medical school in San Francisco in 1865 led to the suspension of teaching for a time. But after five years it was reinstituted, again as the Medical Department of the University of the Pacific. Two years later, in 1872, the school became known as the Medical College of the Pacific and after another decade members of its faculty formed Cooper Medical College under the guidance of Dr. Levi Cooper Lane. Lane was not only the founder, but the Medical School Building at Sacramento and Webster Streets was built with his personal funds. Cooper Medical College, with its subsequently built hospital, thrived for over the next quarter century when in 1908 the Stanford University Board of Trustees adopted President David Starr Jordan's recommendation that the Cooper Medical College be accepted as its school of medical research. The above transitions were not without hardship in human terms[1]; but then is the development of any worthwhile institution without trial?

The First Half Century (1909-1959)

During its first 50 years, pre-clinical instruction at the Stanford University School of Medicine was conducted on the Stanford campus near Palo Alto, whereas clinical instruction took place in San Francisco, some 40 miles away. The initial pre-clinical faculty of seven consisted of Jenkins (Physiology), McFarland (Histology), Meyer (Anatomy), Price (Zoology), Snow (Hygiene), J. Stillman and Swain (Chemistry). In San Francisco, the original faculty of eight were Barkan (Eye), Cheney (Medicine), Gibbons (Obstetrics), Hirschfelder (Medicine), Ophuls (Pathology), S. Stillman and Rixford (Surgery), and Ray Lyman Wilbur (Clinical Medicine). The first seven of these clinicians were appointed from the Cooper faculty.

Within the first few years, several outstanding newcomers joined the faculty. One of these was the bacteriologist Hans Zinsser, who, of his 1910-1913 experience at Stanford, wrote in his autobiography[2]: "Golden days at Stanford! Adequate equipment, small classes composed largely of men who had worked their own ways to an education, complete independence of teaching and research. Most of the faculty, indeed, a little stodgy as usual, but among them a few brilliant spirits . . . Jordan, himself, we grew to love. He was actually far from a tyrant; rather a dreamer, bullied by a turbulent and largely radical faculty . . . Happy Stanford! The lovely Santa Clara Valley, indescribably peaceful in its golden sunshine; the fragrance of blossoms from its orchards; and the evening fog streaming from the big redwoods silhouetted on the crest of the coast range. Freedom for work, freedom from urban interruptions, few but good students, and cheap horses."

During Dr. Ray Lyman Wilbur's deanship (1911-1916), the Medical School obtained a healthy start. Among the educational innovations was a decrease in required course work, allowing 100 hours for electives during the four years. After leaving his Medical School post, Dr. Wilbur continued to serve his profession, his university and his country well.[3] Among the many offices he held were the presidency of the American Medical Association (1923), the presidency of Stanford (1916-1943), and the United States Cabinet post of Secretary of the Interior (1929-33). It is of interest to note that when, in his sixty-eighth year, Dr. Wilbur was made Chancellor of Stanford, Dr. Donald Tresidder, another physi-

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Reprint requests to: Dean's Office, Stanford University School of Medicine, Stanford 94305.

*University of the Pacific, chartered in San Jose in 1851 as California Wesleyan University, was also the State's first.

cian (as had been David Starr Jordan as well) became President of the University.

Dr. William Ophuls' service as Dean began in 1916 with the disruption caused by World War I and continued through the height of the Depression in 1933 with its attendant disruptions. Notwithstanding, expansion of the Medical School faculty and student body was steady during the deanship of Dr. Ophuls. Indeed, reaching the zenith of their practice and professional influence today are the generation of students who learned from the teachers brought to the faculty by Dr. Ophuls. Such teachers include: Professors Barnett, Bloomfield, Chamberlain, Eloesser, Emge, Faber, Hanzlik, Hewlett, Holman, Martin, Mehrtens, Newell, Reichert, Schultz and Weymouth. Despite the Depression, the tuition was increased to $115 per quarter. In 1931, with the establishment of straight internship, the house staff consisted of 15 interns and 21 residents. The splendid building plans of the '20s, however, had crashed along with the stock market in 1929.

At about the time when the first glimmer of an upward economic trend began, in 1933, Loren R. ("Yank") Chandler became Dean. That same year, the student body was increased to 60 in the entering class, a figure essentially held level since then. The peaceful progress of the late '30s terminated abruptly with the Declaration of National Emergency and the institution of selective service in 1940. The immediate effects of World War II on the students and the faculty alike were evident. Together with the other medical schools in the nation, Stanford went on a continuous teaching program, known as the nine-nine-nine plan. About one-third of its faculty of nearly 60 were away on military leave. With the many returning veteran physicians seeking post-graduate training, the house staff was expanded in the immediate post-war period to 17 interns, 49 residents and 38 fellows.

From very nearly the time of its establishment as a Medical School, there had been repeated discussions concerning the advisability of bringing together the pre-clinical and clinical teaching. Though there was little disagreement that such a move was advisable, there was polarization of interested persons on the question as to whether it was better to unify the Medical School in San Francisco or on a campus site at Stanford. Discussions and divisions of opinion on this subject became increasingly prominent in the late '40s and early '50s. With strong support from University President J. E. Wallace Sterling, in July of 1953, the Stanford Board of Trustees announced the intention to establish the Medical School on the University campus. Thirty years after his graduation from the Medical School and 20 years after his becoming the Dean, "Yank" Chandler, one of the most respected men in Stanford's history, left the deanship.

Under Dean Windsor Cutting (1953-1957), there was a flurry of planning and activity to implement the intent of the Board of Trustees. Seemingly overwhelming obstacles were met head-on. With his characteristic idealism and imagination, Dr. Cutting dealt with the diverse factors entailed in "the move." During this period, the University and the City of Palo Alto entered into an agreement to construct and operate jointly the Palo Alto-Stanford Hospital. Under terms of the agreement, the City of Palo Alto took title to one of the two patient care pavilions and the University to the other. Certain central facilities, including the operating room, laboratories, and some specialized patient care units, were jointly owned. A Hospital Board, made up of equal numbers of Palo Alto and University appointees, was to be responsible for the hospital operations. In addition, an agreement was made with the Veterans Administration, and, in a friendly condemnation suit, several acres were acquired by the Veterans Administration on the campus of the University (albeit some four miles from the Medical Center proper) on which to build extensive hospital facilities for use in Stanford research and in the teaching of Stanford medical students and residents. By September of 1956, ground had been broken for the Stanford Medical School campus. That year, tuition was raised to $355 per quarter and that year, too, the Stanford Hospital had a house staff of 107. The turbulent portion of the transitional years of planning, fund raising and building lasted well into the first two years of the deanship of Dr. Robert Alway (1957-1964).

Commenting on "the move," Dr. Loren Chandler said[4]: "There has been much talk of moving the Medical School, but unfortunately this school cannot be moved. The school on Clay Street has lived a useful and worthy life. Many superior physicians, considerable research of fundamental value and two great groups of teachers have made Stanford Medical School's reputation outstanding during the past 40 years. Our school has been recognized as superior, not only in the United States but in many foreign countries. The countdown on all these activities of the school in San Francisco has already started. The old school, as it has been known, will close this summer. A new school, new in location, philosophy, objectives, curricula and with many new faces on the faculty, will be born in September 1959 on the Stanford campus. The King is dead. Long live the King!"

The Past Decade

It is probably correct to say that there was at least as much change in the transition of Stanford on Clay Street to Stanford on Pasteur Drive as there had been in the transition of Cooper to Stanford. Continuing growth and development in nearly every element of the Medical School during the past ten years is even more striking. These changes involve the students and faculty, the curriculum, financing and physical facilities as well as relationships between the Medical School and other institutions.

In 1959 the Medical School moved into a magnificent complex of seven buildings under one roof designed by the noted architect Edward Durell Stone. Since then, a Clinical Sciences Research Building has been added to the $28 million center, and as will be detailed, the University has acquired full ownership of the Medical Center that houses the Stanford University Medical School as well as the Stanford University Hospital and Clinics. Last year, the 583-bed Stanford University Hospital admitted 22,500 patients and handled 19,400 visits in its emergency room. Some 75,200 x-ray examinations and 31,900 x-ray therapy procedures were performed. There were nearly 480 autopsies, representing a 61 percent consent rate. The total of outpatient visits to the Stanford University Clinics was 103,300.

During the past ten years, the full-time faculty has increased in number from about 100 to nearly 300. Among the many important additions were two recipients of the Nobel Award, Drs. Arthur Kornberg and Joshua Lederberg. The faculty of the clinical departments have changed from a "geographic" to a "true" full-time basis. Their individual income is not directly dependent on the volume of private practice; rather it reflects their total contribution to teaching, research and administration, as well as patient care. A voluntary faculty of nearly 800 contributes heavily to the clinical teaching program.

The Medical School faculty is deeply involved in research, and last year received nearly $11 million in grant awards. The source of such support represents a decided shift in funding patterns toward increasing financial suport by the Federal Government. Fields of investigation include chemical basis of heredity and cell differentiation, immunology, transplantation, radiobiology and neuroendocrinology, as well as each of the more conventional substantive medical disciplines. It is noteworthy that many of the basic research endeavors have subsequently found clinical application. For example, the linear electron accelerator, developed by Stanford physicists and engineers, has been adapted for cancer therapy by Stanford radiologists headed by Dr. Henry Kaplan. Also the laser, whose co-inventor is a Stanford physicist, has been adapted by Stanford physicians for the treatment of detached retina. Stanford also has one of the most successful open-heart surgery programs in the nation. Basic heart transplantation techniques currently in clinical use throughout the world were developed in Stanford laboratories under the direction of Dr. Norman Shumway.

Although the size of the medical student body has remained about the same during the past decade, there has been an ever-increasing resident staff that reached nearly 260 last year. The number of applicants for Medical School and for residencies has constantly increased and the quality of applicant as measured by the usual criteria is better than ever. Indeed, Stanford's educational programs attract some of the best candidates in the country.

One of the most important of the several innovations associated with the move of the Medical School was the inauguration of a new curriculum that has become known as the "Stanford Plan." This program in medical education was based on three major concepts. The first of these is that all education is a continuum. The second belief is that the growth of medical science is so great and continues at so rapid a pace that its comprehensive coverage cannot be achieved. At the heart of the study of medicine, however, lies a core of medical knowledge which should be presented to all medical students, irrespective of their eventual choice of medical careers. The third attitude is that the student of medicine has passed beyond the stage of his education where the mere acquisition of facts can be defended. Rather, he should be encouraged to learn in terms of approaches to problems in medicine rather than in terms of the acquisition of technique or the accumulation of data at the expense of interpretation. Basic to this is the need to understand the scientific method. The most striking feature of that curriculum was the provision of a five-year educational experience during which there were sizable portions of free time as well as built-in elective time to complement the core material. This program, described in detail by Stowe,[5] represents the forerunner of the medical school curriculum of the future.

The dramatic developments and growth of the School of Medicine that took place largely during the deanship of Dr. Alway made it apparent that the hospital organization, as originally established in the '50s, had numerous deficiencies. Certainly a single administration trying to serve two owners made for difficulties in both the day-to-day operation and in long-term planning for hospital development. This was so despite the efforts of a group of outstanding, public-minded citizens who comprised the hospital's board of directors and who discharged their responsibilities in admirable fashion.

After a year under the acting deanship of Dr. Sidney Raffel, in 1965 Dr. Robert J. Glaser was appointed Vice President for Medical Affairs and Dean of the School of Medicine. Under his leadership, the University began an intensive study of the hospital situation with a view toward projecting a plan whereby a University Hospital, in the best sense of the word, could be developed. After detailed examination was completed, it was decided that the University should attempt to acquire the City's hospital holdings. In the late Spring of 1968, the negotiations with the City of Palo Alto toward attainment of the above objective were completed and an agreement was reached between the City of Palo Alto and Stanford University, defining terms whereby Stanford would acquire all of the City's hospital facilities. In turn, the University undertook to provide appropriate patient care facilities for the citizens of Palo Alto and surrounding area, as well as to include, in a unified University Medical staff, the physicians who formed the Palo Alto Medical Staff of the Palo Alto-Stanford University Hospital.

On 1 July 1968 the Stanford University Hospital became an entity, and the Board of Trustees of the University at the same time designated the entire center, including both the School of Medicine and the Hospital, as the Stanford University Medical Center. This development can be said to round out the first phase of the University's program in medical education on the campus.

The Future

Within the framework of full integration with a vigorous University that is dedicated to mankind, the future of the School of Medicine generally looks bright. Lest the glimpse into the crystal ball tend to be too distorted by this spirit of optimism, comments on future developments will be limited to those areas in which at least the preliminary blueprints exist. Since the areas of central concern of the Medical School are complex and are inexorably interwoven, the order in which they are presented is not necessarily an indication of their priority.

Certainly the education of medical students is a prime function of the Medical School. Today, there are over 2,000 applicants for the 64 first year positions and there is every indication that the applicant figure will climb about 10 percent each year. Furthermore, on a competitive basis, with the notable exception of one other institution, students who are accepted to both Stanford and other Medical Schools prefer to come to Stanford. This trend, too, will likely continue. The overall quality of the students is increasing as to both their abilities and their educational backgrounds. Each year, students matriculate much better prepared, particularly in their special areas of interest; and, by and large, they are earlier aware of their longer term goals within medicine.

In the light of the quality of students being attracted to Stanford, the curriculum that was pioneered only ten years ago is being replaced with one that more nearly approaches the objective of a tailor-made program for each individual. The curriculum being adopted conceives a medical education as a graduate program during which the student is responsible for assimilation of an identifiable body of knowledge, pursued with maximum opportunity for independent study and research and modified selectively in accordance with career objectives. The educational program of the individual student is designed and carried out in accordance with certain definite policies and procedures in order that an appropriate balance and sequence may be achieved. The policies and procedures involve advisory groups of faculty and student members for each student to consult both collectively and individually on the selection and implementation of his program. In order to graduate, the student shall have been registered in an approved School of Medicine for a minimum of four academic years, he shall have demonstrated factual knowledge and understanding of both preclinical and clinical subjects by passing parts I and II of the examinations conducted by the National Board of Medical Examiners, and he shall have completed a course plan consisting of the minimum of 4,500 course hours, which has been approved by the curriculum committee as appropriate for the goals of the School of Medicine and the background and career goals of the student. This new curriculum gives the student graduate status, is flexible, and seeks to establish a clear interrelationship between medical science and medical practice. Specifically, the core curriculum of the past ten years has been redefined with increased elective opportunities for satisfying requirements in subject areas. Each student is allowed to develop a study plan in accordance with his abilities, background, experience and personal career interest. There is little question that, once again, Stanford is likely to lead the way with this current revision, extension and elaboration of the Stanford Plan of Medical Education pioneered in 1959.

Stanford Medical School will continue to examine other aspects of its educational role. An immediate problem is how can Stanford best participate in increasing the nation's physician supply. In this context, what is Stanford's optimal role in education of persons from educationally disadvantaged minority groups? With the current pressures, both internal and external, it appears likely that the class size will be increased soon. In addition, special recruitment programs for minority students are likely to have been established by the time this is in print.

It must be apparent that the new curriculum makes many more demands upon faculty time and energy. Yet, the rate of increase of faculty has begun to level off substantially, a trend that appears likely to continue in the light of Federal economies regarding support for basic medical research and medical education. It appears unlikely that acquisition of new endowed chairs will be sufficient to keep pace with the needs. If current trends continue, new methods of financing along with new economies must be developed.

In order to maintain and improve excellence in the area of clinical care, high quality of research in both the basic and the clinical sciences, and responsible innovations in education, Stanford will continue its building program. A master plan, with multiple input, including the proposals of a Medical Facilities Planning Group under the leadership of a systems engineer, is now in its 14th month of development. There is a need to increase the basic science facilities of the School of Medicine and the clinical facilities of the University Hospital, as well as to develop new approaches to patient care that will enhance quality and at the same time achieve economies. These facilities will be built.

The School of Medicine is increasingly addressing itself to social and economic issues as they relate not only to medical student education, but to graduate and continuing medical education, as well as to health care more generally. The Medical School is deeply concerned about rising costs of medical education and of health care. It is acutely aware of the problems related to the distribution and delivery of health care services. Recent Federal legislation in the form of the Regional Medical Programs enables Stanford to actively pursue solutions to these problems at least to the extent of assisting to make available to the entire community within its designated area, through cooperative arrangements, the best possible patient care for heart disease, cancer and stroke. It appears likely that the Regional Medical Programs will greatly stimulate Stanford's future participation in continuing medical education. Another Federal law known as the Veterans Administration Sharing Bill promises to be of substantial assistance in raising standards of medical care. Stanford will be a leader in its implementation.

After all is said and done, the future is with our young. Members of the faculty will serve to a substantial extent as professional models, and to some degree as personal examples with whom the students will identify. Although the medical faculty is replete with examples of professional and scholarly excellence and leadership, an unusual current historical circumstance deserves special mention. This year, Dr. Dwight L. Wilbur (Clinical Professor of Medicine) is President of the American Medical Association; Dr. Philip R. Lee (Clinical Assistant Professor of Medicine) is Assistant Secretary for Health and Scientific Affairs of H.E.W.; and Dr. Robert J. Glaser (Professor of Medicine) is President of the Association of American Medical Colleges and, at the time of this writing, is Acting President of Stanford University. It is the hope of the faculty that future graduates of Stanford Medical School will surpass them in professional and scholarly excellence and leadership, and as just plain, responsible human beings. Stanford University School of Medicine faces the future with confidence that its students can and will meet the challenge implied by these hopes.

THOMAS A. GONDA, M.D., Associate Dean

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GUNSHOT OR KNIFE WOUNDS OF THE URETER

"Unless the surgeon has a high degree of suspicion, or notes the presence of hematuria or an expanding mass in the abdomen, he frequently will not recognize traumatic division of the ureter by gunshot or sharp instrument right away. If he is suspicious, he should do high dose intravenous pyelography or retrograde pyelography. If the patient is in shock when an intravenous pyelogram is done, the extravasation may be missed because of decreased renal blood flow and resultant poor x-ray medium excretion by the kidney. Retrograde pyelography is therefore more reliable. Gunshot and knife wounds are usually associated with bowel perforations and other visceral trauma and require open operation. In gunshot perforations of the ureter, it should be remembered that adjacent ureteral wall for about 1 to 1.5 cm above and below the defect may have been intrinsically damaged by both heat and blast effect; and although it may look normal, this segment of ureter should be excised back to free bleeding tissue. Anastomosis may be made with a splint in place provided there is no tension on the suture line. This precaution is not necessary in the case of knife wounds. While urological evaluation is important in the patient with a knife or gunshot wound, priority has to be given to any condition that is more of an immediate threat to his life."

—WILLIAM R. SMART, M.D., San Francisco

Extracted from *Audio-Digest Surgery,* Vol. 15, No. 20, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

California
Medicine

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EDITORIAL

New Scientific Stature

It has been years since the California Medical Association has been looked upon by its dues paying members as an organization of scientific stature. Yet, by its constitution and bylaws the CMA is basically an association of component local medical societies whose physician members are banded together for scientific improvement. CMA leaders of a decade ago recognized that if the organization were to remain true to this purpose some steps should be taken to strengthen its activities and productivity in this area of fundamental concern to the membership. In 1963, in response to the recommendations of an ad hoc committee that had Dwight L. Wilbur as chairman, the House of Delegates authorized the establishment of a Scientific Board within the CMA structure.

The results of this wise and far-seeking action are now beginning to appear and some of the evidence is to be found in this issue of California Medicine. The story of the Scientific Board, an organizational instrument unique to the CMA, is recounted by its respected and beloved first chairman. The Scientific Board has had distinguished leadership since its inception, and many dedicated physician scientists have served not only on the board itself but also on its various committees and subcommittees. A major payoff of this new organizational approach to medical science is foreshadowed by the high caliber of the scientific program for the coming Annual Session which is printed in the section immediately following page 106 of this issue.

Each year since the Scientific Board came into being the scientific program of the Annual Session has improved in quality, each standing on the shoulders of its predecessors. This year, more clearly than ever before, it is a measure of the growing scientific stature of the California Medical Association. Any dues paying member will be well rewarded, scientifically and otherwise, if he can find an unsuspecting colleague who will watch over his practice while he attends this worthwhile meeting.

Management of Rheumatoid Arthritis

It is not through a lack of effort that our medical armamentarium does not contain a consistently effective treatment for peripheral rheumatoid arthritis. Individual physicians as well as cooperating clinic studies have used drugs, physiotherapy and sage advice to the patient in almost every conceivable combination. Inevitably we find that some patients' disease remits with almost no care while in other cases the inexorable progression of articular destruction and point deformity bears painful witness to how difficult it is to find a cure without knowledge of cause and pathogenesis.

To distill that which is practical and useful to the physician in the care of patients with rheumatoid arthritis from the mass of more or less controlled clinical studies was the task set by Drs. Kamin and Multz in this issue of California Medicine.

Beginning with the problem of how to instill a positive and constructive attitude in a patient faced with a chronic and potentially crippling disease, the authors next deal with much neglected nondrug modes of therapy. It is difficult to make prosaic events such as mid-day naps and weight reduction seem as significant to physicians and patients as some new variation of an old drug. Physical therapy has its enthusiasts and these authors must be counted among them. Their opinion that "simple range of motion exercises religiously practiced can prevent ankylosis" goes beyond what must be considered a conservative position on the benefits of applied physiotherapy.

It is to drug therapy that the authors as well as most physicians devote major attention. Although generally conservative about the efficacy of drugs in common use, they at times advocate rules of therapy which are not beyond the scope of controversy, such as "the appearance of iritis or scleromalacia perforans make the use of steroids mandatory." It must be noted that these unfortunate complications frequently occur during adrenocorticosteroid therapy and, like other manifestations of overt vasculitis in rheumatoid arthritis, may in part be attributable to the steroids themselves.

The bewildering tendency of rheumatoid arthritis to undergo spontaneous remissions and exacerbations continues to confound those attempting to design proper controlled studies. The physician in practice will find much in this article by Drs. Kamin and Multz that is practical and useful. Inevitably, however, there will continue to be a folklore of rheumatology which will mock rational approaches to therapy until the pathogenetic mechanisms of this distressing disease are finally elucidated.

Biologic Science and Human Equality

THE SUBJECT OF quality and inequality among humans is a timely one. In science there has been an enormous effort to overcome biological inequalities which cause one human to reject the organs of another and in society there has been an enormous effort to overcome the social, economic and political inequalities — and all of this in spite of the fact that both seem to be inherent in human nature and the human condition. In any case the results to date have been disappointing, even frustrating. At first glance these kinds of differences among humans may seem unrelated but perhaps they are not.

The concept of political equality apparently took root in the late 18th century at the time of the American and French revolutions and it seems to have been dependent upon progress in science and technology for its growth and development. Legislation has been a principal means to promote equality and it seems always to have followed technologic progress. For example it may be argued that the 19th century invention of the cotton gin made legislation to free the slaves a practical matter. Later an unrestrained exploitation of the technological industrial revolution polarized poverty and riches to such an extent that some kind of equalizing legislation became necessary in the early 20th century. This took the form of anti-trust laws, labor laws, graduated taxes and public relief for the needy. World War II produced an enormous burst of scientific and technologic progress and for the first time much of the intellectual and political leadership of the nation became convinced that our technology had finally reached the point where the ideal of human equality had become practically attainable. The sequel to this was an attempt, again through legislation, to lessen and if possible abolish social, economic and political inequality. Perhaps predictably from the standpoint of biologic uniqueness, the results have fallen far short of the expectations, and there is now a new restlessness throughout the land and indeed throughout the world.

In this new restlessness there is more than a suggestion of a fundamental change in human aspirations. It seems more than conceivable that the traditional expectation of social, economic and political equality may be about to undergo some evolutionary revision. Again it would appear that scientific and technologic progress sets the stage. Modern science recognizes that each human being is biologically unique with individual characteristics and an individual potential for creativity and fulfillment. It seems quite possible that the 20th century is on the verge of coming to recognize the fundamentally biologic nature of human society just as the 19th finally accepted the biologic nature of man himself. Society is beginning to acknowledge, albeit slowly, that sameness is not a human characteristic. It appears that the demands for equality among humans are now beginning to give way to demands for an equal chance for health, freedom, more relevant education and more in the way of personal fulfillment. If these aspirations for personal fulfillment recognize the equal rights of others, they are at once both biologically and socially sound.

There is a great opportunity in this change for real responsible human progress. There is also chance of disaster. Power and privilege are potent instruments which in the hands of special interests with skilled leadership can jeopardize the rights of others and even threaten the integrity of the complex technologic society without which the hopes for greater personal fulfillment could only be an empty dream. At so critical a time, reason and not emotion must rule. The change must be evolutionary, not revolutionary; and the outcome must be sound biologic and social progress and not disaster. Steady, responsible yet flexible hands are needed at the helm and physicians must stand ready to help. As the truly biologic nature of society becomes more clearly recognized by the public, there will be more attention given to the biological characteristics of the body politic and the biological nature of the humans who comprise it. As this occurs the physician, because of his knowledge of the nature and behavior of human beings in both sickness and in health, will inevitably become increasingly involved. It is not too early for the profession to get into training for this new responsibility as human aspirations rise to match the potential of this new age of science.

Medi-Cal and the Legislature

The California Legislature may be expected to give careful scrutiny to the Medi-Cal program during the 1969 session. This is as it should be. The Legislature is responsible for examining the allocation of the state's resources to its needs and to determine whether the best allocation is being made. It is also responsible for determining if there is value received for dollars spent whether this be in health care or whatever.

The federal Medicare legislation of 1965 (P.L. 89-97) established a new approach to the health care of the needy. This became implemented in California with the enactment of A.B. 5 (Medi-Cal) which contained a number of important concepts developed by the California Medical Association and went into effect before the effective date of Medicare. The CMA has since continued its strong support of the principles upon which this program was based and has often gone "the second mile" in cooperation to try to make the program a success. While admittedly not completely satisfactory, the result to date has been what is probably the most effective Title XIX program in the nation.

As the Legislature's review of the Medi-Cal program gets under way it is inevitable that there will be a conflict of values. The ideal in our Medi-Cal law is "to allow eligible persons to secure basic health care in the same manner employed by the public generally and without discrimination or segregation based purely on their economic disability." This approach is unique to California and permits of only one standard of health care for all citizens and quite expectedly it has proven costly, so now it comes into conflict with government's equally important responsibility to control and if possible to reduce these costs. Humanitarian values, scientific values and economic values are all at play and must be kept in reasonable proportion. Care must be taken not to compromise the purpose or impair the effectiveness of a program which so far has led the nation, having handily survived a number of statements tending to discredit it publicly, which may or may not have been deliberately intended for that purpose.

Government bureaucracy and officialdom has a natural, one might almost say a human tendency to believe that it can do what needs to be done better than anyone else. It was therefore quite predictable that attempts would be made to regulate, control, or even take over these expensive government financial health care programs. But the genius inherent in the Medi-Cal program is that it has somehow succeeded in mobilizing the support and effort of virtually all who are involved in the care of Medi-Cal patients to make this law an effective and efficient program for needy citizens. Such a team effort in support of a government financed health care program is quite unprecedented, and when one considers the importance of motivation of health care personnel, whether in the professions or in the industry, to both the ultimate quality and the ultimate cost of the service rendered, it would seem that government would be well advised, both economically and politically, to take steps to strengthen rather than to weaken this kind of motivation.

So far we have had reason to be confident of the wisdom of the California Legislature. Let us hope that this new and unique teamwork in health care can continue. Let us try to solve whatever problems there are with a truly collaborative effort. All Californians will surely benefit, and perhaps the rest of the nation will be shown the way.

LETTERS *to the Editor*

Limits on Pap Smear Under Medicare

To the Editor: At a recent meeting of the Professional Education Committee of the Contra Costa County American Cancer Society, it was brought to our attention that the Medicare Program will allow Pap tests only if they are related to a specific treatment, diagnosis, or problem, . . . "When such tests are to be considered as diagnostic, relating to a specific problem of treatment, the attending physician is usually required to document the need for and circumstances for the tests. If, however, a Pap test is given as part of a routine physical examination, *it will not be allowed or paid for under Medicare.*"

All members of the committee were in agreement that this was not only false economy on the part of Medicare but was indeed a major set-back to the American Cancer Society's program asking all physicians to do annual Papanicolaou smears. It is apparent that this was not written into the Medicare law but is probably a product of a minor official in a local office who is not aware of the implications of this restriction.

We also feel that all physicians should be made aware of this ridiculous proviso and hope you will publish this letter. If you have any suggestions to help us rescind this directive we would be appreciative.

YORKE G. JACOBSON, M.D.
Pittsburg

"Pre-Cancer Test"

To the Editor: Cancer is a dread word whose curabilities are becoming slowly accepted—while the spectral dread of the name and its symbol persist. Public cancer education has two basic objectives:

1. Persuade people who seek prompt medical advice upon the development of certain warning signals.

2. Persuade people, particularly in high risk groups to participate in screening programs.

To achieve either of the above we must address the man in the street in terms regarding cancer as preventable in the clear sense that cancer can be found and dealt with as a pre-cancer. We mean here, the use of the term and image of pre-cancer as a symbolic meaning filled with less dread than the classic term cancer.

With premeditation then, one creates a term pre-cancer to "defuse" cancer of its hoary, century old implications of dread and ego dissolution.

We believe there to be a tremendously significant psychologic difference between the test that will detect pre-cancerous conditions and the test that will detect early cancer and the implications that this latter symbolic term holds.

It is futile to expect large numbers of people to seek medical attention to discover a cancer. The willing patient seeks positive reassurance he has not got cancer. The test or procedure designed to detect *pre-cancer* is, by its very nature, acceptably motivational. The symbolic meaningfulness of cancer and pre-cancer as they affect patient motivation has been neglected to date.

There is much consistent agreement that personal rather than impersonal motivation is most effective in patient and public education.

Physicians represent the most effective source for individual patient search for preventive care in cancer and pre-cancer detection. This fact begs physicians to fuller awareness of the potency, both of their position and their words. It further implores meaningful use of the credibility gap which exists between the public mind and the term "cancer." This large dark gap may be bridged by the use of the word pre-cancer.

Is it not more effective and credible to support and maintain aggressive advice to detect an innocuous pre-cancerous condition than detect a cancer? Thus, *"cancer test"* is a more threatening and self-defeating word than *"pre-cancer test."*

A rose is a rose, is a rose, is a rose. The simple words we use to provide meaningful stimuli to our physician roles as the most dynamic effect in modern cancer prevention. The suggestion is offered that the symbolic communication "pre-cancer test" permits more meaningful stimuli than the words "cancer test."

MARVIN B. RODNEY, M.D.
North Hollywood

REFERENCE

Cancer Detection. U.I.C.C. Monograph Series, Vol. 4. Springer-Verlag, N.Y., pp. 54-74, 1967.

Indwelling Plastic Intravenous Cannulas

To the Editor: On page 423 of the November CALIFORNIA MEDICINE there is a joint statement by the California Medical Association, the California Nurses' Association and the California Hospital Association (Intracaths and the Role of the Registered Nurse).

I am surprised that such a statement backed by three such important organizations will use what I consider to be improper terminology. With all the furor about the use of generic equivalents in advertising of any one product, it seems a little strange to me that the term "Intracaths" is used in the title and in the substance of the statement. I believe the use of the word Intracath in a general sense to describe all indwelling plastic intravenous cannulas is improper. If you will check you will find that Intracath is the trade name for a specific product manufactured by C. R. Bard for their particular brand of catheter.

GILBERT E. KINYON, M.D.
Director of Anesthesiology
Mercy Hospital
San Diego

RESECTION OF ANEURYSMS

"Whether or not a small aneurysm should be resected depends on the general condition of the patient. As the years go by, one sees smaller and smaller aneurysms rupture, and so we tend to recommend the resection of smaller aneurysms; but if the patient has had a myocardial infarction within the past six months or if he has borderline renal function or borderline respiratory function, we would temporize. If a definite aneurysm can be demonstrated in a good risk patient—by palpation or arteriography (which we rarely use for this purpose)—then we would resect it."

—JAMES D. HARDY, M.SC., M.D., Jackson, Miss.

Extracted from *Audio-Digest Surgery*, Vol. 15, No. 19, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

Information

Clinical Uses of Inhibition Of Beta-Adrenergic Receptors with Propranolol

MORRIS STAMPFER, M.D., AND
STEPHEN E. EPSTEIN, M.D.

Material Supplied by the California Heart Association

PROPRANOLOL, THE FIRST clinically useful beta-adrenergic blocking drug, was recently placed on the market after several years of exhaustive clinical trials. On the basis of many investigations, it appears that blockade of the beta-adrenergic receptors may be useful in the treatment of several types of cardiac problems. However, as with any potent drug, the physician must possess full knowledge of its mechanism of action and possible hazards before prescribing. This article is intended as a brief survey of the actions and uses of propranolol for the practicing physician.

Pharmacology

The work of Dale, Ahlquist and others has established the existence of different types of responses to adrenergic stimulation, dependent on the presence of either of two types of receptor sites in the tissues. For example, stimulation of alpha-adrenergic receptors causes constriction of blood vessels, while stimulation of beta receptors causes vasodilation. Only beta receptors are located in the heart, and stimulation of these receptors results in an increase in the heart rate and the force of cardiac contraction. The endogenous catecholamines, epinephrine and norepinephrine, stimulate both alpha and beta receptors, while the catecholamine isoproterenol stimulates beta-adrenergic receptor sites exclusively. Although alpha-adrenergic blocking drugs have been known for many years, propranolol is the first generally available drug which antagonizes the action of catecholamines at the beta-adrenergic receptor sites, thus causing slowing of the heart rate and a decrease in the force of cardiac contraction.

Clinical Uses

1. *Angina Pectoris*

Angina pectoris is due to a disproportion between the O_2 requirements of the myocardium and the O_2 supply so that the supply of oxygen is inadequate to meet myocardial metabolic demands. In theory, angina can be relieved either by increasing oxygen delivery or decreasing metabolic requirements. Since both heart rate and the force of contraction are important in determining the amount of O_2 required by the heart, propranolol, by decreasing these parameters during exercise, is often successful in relieving angina that is refractory to the most commonly used drugs. The dose required is highly variable and is best ascertained by starting with a small dose such as 10 or 20 mg by mouth four times daily, and increasing gradually until attacks of angina are substantially reduced in frequency. Doses of 400 mg daily or more have occasionally been used, although the most commonly required dosage ranges from 120 to 240 mg daily. Very close observation of the patient is necessary since congestive failure may appear. Such symptoms may often be controlled with digitalis glycosides and diuretic agents. However, if these interventions are not successful in controlling symptoms of failure, propranolol must be discontinued.

2. *Arrhythmias*

Propranolol can be used in the treatment of various cardiac arrhythmias; its beneficial effects are due not only to beta-adrenergic blockade, but in certain arrhythmias to a quinidine-like action as well.

Propranolol may abolish arrhythmias caused by digitalis intoxication, including frequent premature ventricular contractions and ventricular tachycardia. It should be stressed, however, that there is no evidence that propranolol is superior to some of the other commonly used antiarrhythmic agents.

In arrhythmias not due to digitalis, such as atrial fibrillation or atrial flutter with rapid ventricular response, propranolol usually can be relied upon to slow the ventricular rate. Recurrent attacks of paroxysmal atrial tachycardia may occasionally be reduced in frequency or prevented by propranolol, although sufficient information to assess long-term results is not yet available.

Associate in Medicine, Albert Einstein College of Medicine, Bronx, New York (Stampfer); Acting Chief, Cardiology Branch, and Chief, Section on Circulatory Physiology, Cardiology Branch, National Heart Institute (Epstein).

From the Cardiology Branch, National Heart Institute, Bethesda, Maryland.

When emergency treatment is required, propranolol should be given intravenously in doses of not more than 0.5 mg every three to four minutes until the desired effect is achieved or signs or symptoms of worsening cardiac decompensation are noted. The drug should not be used in complete atrioventricular block with idioventricular rhythm (unless a cardiac pacemaker is in place) since electrical activity may be slowed further or arrested.

3. *Idiopathic Hypertrophic Subaortic Stenosis*

Propranolol has been found to be beneficial in many patients with idiopathic hypertrophic subaortic stenosis (IHSS). The exercise tolerance of patients, whose primary symptom is angina pectoris, has been improved by propranolol, and the frequency of syncopal episodes and of arrhythmias can be reduced in other patients. The reason for this improvement probably is due to the fact that obstruction to left ventricular outflow in IHSS is made worse by drugs or maneuvers that increase the contractile state of the heart, such as isoproterenol or exercise. Propranolol, by decreasing sympathetic stimulation of the heart, decreases this obstruction. This change is less marked at rest, when there is normally little sympathetic stimulation present, but becomes more significant during exercise.

It should be stressed that in patients with IHSS and congestive failure, the drug may produce deleterious effects just as in patients with other types of heart disease who have signs and symptoms of cardiac failure.

Side Effects and Contraindications

By interfering with sympathetic stimulation to the heart, propranolol decreases the cardiac output response to exercise in normal subjects, and thereby impairs their capacity to perform intense exercise. This finding demonstrates the significant role of the sympathetic system in the cardiac response to the stress of exercise. Propranolol also alters the diurnal pattern of sodium excretion in normal subjects and in patients with mildly impaired cardiac function. However, in patients with severe cardiac decompensation its administration may cause frank retention of sodium and fluid, changes resulting in progressive edema accumulation and symptomatic deterioration. Thus, in patients with heart disease whose cardiac reserve is diminished and who depend upon sympathetic support to maintain compensation, inhibition of cardiac sympathetic stimulation may lead to severe and sometimes irreversible symptoms of cardiac failure.

Other major side effects that have been reported are severe hypoglycemic reactions occurring in patients taking insulin or oral hyperglycemic agents, and acute pulmonary insufficiency due to bronchospasm, a complication that may occur in patients with obstructive airway disease.

Summary

Blockade of the beta-adrenergic receptors is of significant benefit in selected patients with various types of heart disease. Angina pectoris, digitalis-induced arrhythmias, atrial fibrillation and flutter, and idiopathic hypertrophic subaortic stenosis are conditions in which this drug may be useful. However, caution and continued close observation of the patient is always necessary because removal of sympathetic support to the failing heart may result in severe cardiac decompensation. Propranolol and other beta-adrenergic blocking drugs should not be administered to patients with congestive heart failure that does not respond to digitalis glycosides and diuretics, and to patients with atrioventricular block, unless a cardiac pacemaker is in place. In addition, they should be given with extreme caution to patients with obstructive airway disease and to patients taking insulin or oral hypoglycemic agents.

California Medical Association

Council Highlights

Highlights of the Actions of the California Medical Association Council Meetings, September 28 to 29, Los Angeles and November 8 to 9, San Francisco

This summary is published so that CMA membership may be advised in brief of the actions of the Association's Council. It covers only major actions and is not intended as a detailed report. Full minutes of these meetings are available upon any member's request to the CMA office.

547th Meeting, September 28 to 29, 1968, Los Angeles

Propositions 3 and 5 in the November 5 general election were endorsed. Proposition 3 provides for a $250,000,000 bond issue for construction of state colleges, universities and urban school facilities. Proposition 5 authorizes the legislature to grant authority to a designated public agency to insure or guarantee loans for the construction, improvement or repair of nonprofit or public hospital facilities.

A request to the CMA Committee on Insurance and Prepayment was approved. The committee will study what AMA is doing about improvements in —and standardization of — insurance claims forms. The study is sought in order that the forms can be used more effectively for electronic data processing. A report will be made to Council.

Recommendations of the CMA Commission on Public Agencies approved were:

- The hyaline membrane detection program of the State Department of Public Health be studied by a subcommittee of the CMA Scientific Board.
- CMA vote to support adequate funding for the Department of Public Health Virus Laboratory during the 1969 legislative session.

CMA co-sponsoring a workshop on School Health Education was approved. In addition, a total of $800 from the budget of the CMA Committee on School and College Health for this project was approved.

A conference on "Medicine's Role in Aviation Safety" was approved. It will be sponsored by the CMA Commission on Community Health Services.

Donations to Physicians' Benevolence Fund were urged by Council. The donations would be in memory of their late colleagues.

A meeting of the CMA Executive Committee with physician representatives of both California Blue Shield and Foundations for Medical Care was approved. The purpose of the meeting will be to plan for two physician-sponsored prepayment and insurance groups.

The concept that hospital medical staffs have the same voice in the appointment of hospital-based physicians as in appointments to clinical services was approved by Council.

CMA Council reiterated its policy on utilization review and urged component societies to be more active in implementing this policy.

CMA Medical Staff Survey Committee recommendations approved were:

- Direct the CMA Committee on Committees to draw up selection procedures for membership on the CMA Medical Staff Survey Committee, based upon a physician's previous experience as a past chief of staff, or chairman-member of a major committee of a hospital.
- Start the practice of charging each hospital for a survey—the actual amount to be determined on the basis of a cost analysis of past survey expenses. Monies derived from the survey will be used toward payment of staff and professional expenses.
- Compensate members of the Medical Staff Survey Committee for their participation in committee activities.

"Family Life Education" was referred again to the CMA Commission on Community Health Services and the CMA Committee on School and College Health.

Expansion of the CMA film library to include "Medicine of the Sixties" series was approved.

Television for the 1969 CMA Annual Session was approved. A program schedule will be carried in the CMA Annual Session *Daily Bulletin.*

Additional guidelines for performing organ transplants were approved by Council. They were aimed primarily at obtaining prior agreement between the coroner (or medical examiner), physician performing the transplant and representatives of the appropriate county medical societies. The guidelines supplement those approved by CMA Council last March.

Extension of the state's cancer quackery law was approved. Council also voted in favor of removing the law's time limit—it ends in December 1969.

548th Meeting, November 8 to 9, 1968, San Francisco

A policy statement on "The Relationship between Clinical Laboratories and the Practices of Medicine" was adopted. It is as follows:

> "By California law, direction or supervision of the Clinical Laboratory may be carried out either by a physician or a licensed bioanalyst. The actual performance or a test, regardless of method is a technical procedure and thus not exclusively reserved to Doctors of Medicine. The Clinical Laboratory is a vital part of the physician's diagnostic armamentarium so that ultimate responsibility toward the selection of the laboratory, choice of test, interpretation and application of the results is his.
>
> The precepts of medical ethics that apply to advertising also apply to clinical laboratories."

Drafting of a model "informed consent" form was approved by Council. A recommendation was also approved that all physicians use the document. It will be drawn up by the CMA Medical Review and Advisory Committee.

The Component Society Officers' Conference as an annual CMA activity was approved.

An allocation "up to" $5,000 for the 1968-69 budget of the ad hoc Committee on Health Care was approved. The committee will study in depth fundamental problems in changes in the organization and delivery of health care services and their impact on quality, costs and availability.

Support by the CMA delegation to AMA on its proposal for the concept of graduated income tax credits was approved. In essence, the graduated income tax proposal would provide tax relief on a graduated income tax basis or would enable the purchase of health insurance (for the lowest income groups) through the use of vouchers.

Formation of an ad hoc Committee on Monterey Workshop recommendations was approved. Members are Kash Rose, M.D., chairman; Thomas Elmendorf, M.D.; Stanley Moore, M.D.; Frank Rogers, M.D., and John T. Saidy, M.D.

CMA Medical Staff Survey Committee should serve as the official examining body of hospital medical staffs throughout the state in order to satisfy the annual inspection requirements of Medi-Cal and Medicare laws. This policy, recommended by the Council Workshop, was adopted by Council and referred to the CMA Commission on Hospital Affairs for action.

Other Council Workshop recommendations approved by Council were:

- Medical Staff Surveys include extended care facilities and each county medical society have an Extended Care Facility Review Committee. These recommendations were referred to the Commission on Hospital Affairs for implementation.
- CMA inform component societies that the change in the Medical Practice Act of 1965 allows restriction of the physician's professional activities without suspension or revocation of license.
- Collaboration be increased between specialty societies and the scientific sections of CMA, with use of and/or creation of advisory panels to all sections.
- Component societies should be encouraged to involve new physicians in society activities with subsequent recommendations for appointments to CMA committees.
- The name of the Committee on Committees be changed to Committee on Nominations and its meetings open to all Council members.
- One or more Council Retreat workshops be held annually.

In Memoriam

Alpers, Nathan, Beverly Hills. Died 25 November 1968 in Los Angeles, aged 56. Graduate of Tufts College Medical School, Boston, 1939. Licensed in California in 1946. Doctor Alpers was a member of the Los Angeles County Medical Association.

◆

Anderson, Robert Ernest, San Francisco. Died 5 December 1968 in San Francisco, aged 46. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1947. Licensed in California in 1947. Doctor Anderson was a member of the San Francisco Medical Society.

◆

Arnold, Walter Frank, Long Beach. Died 29 October 1968 in Long Beach, aged 67. Graduate of Tulane University School of Medicine, New Orleans, La., 1927. Licensed in California in 1929. Doctor Arnold was a member of the Los Angeles County Medical Association.

◆

Beattie, Arthur S., Los Angeles. Died 14 November 1968 of injuries sustained in an automobile accident near Roberts, Idaho, aged 49. Graduate of Northwestern University Medical School, Chicago, 1948. Licensed in California in 1950. Doctor Beattie was a member of the Los Angeles County Medical Association.

◆

Betenson, Thomas E., Sun City. Died 3 November 1968 in Hemet, aged 79. Graduate of Western Reserve University School of Medicine, Cleveland, 1919. Licensed in California in 1920. Doctor Betenson was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

◆

Blei, Nicholas, Los Angeles. Died 5 November 1968 in Los Angeles of heart disease, aged 51. Graduate of Universita Karlova Fakulta Lékárska, Praha, Czechoslovakia, 1945. Licensed in California in 1962. Doctor Blei was a member of the Los Angeles County Medical Association.

◆

Booth, Myron Murray, St. Helena. Died 12 November 1968 in St. Helena, aged 75. Graduate of University of California Medical School, Berkeley-San Francisco, 1920. Licensed in California in 1920. Doctor Booth was a retired member of the Napa County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

Curro, Florence Louisa, San Francisco. Died 6 November 1968 in San Rafael, aged 61. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1932. Licensed in California in 1932. Doctor Curro was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

◆

Friedman, Melvin, Oakland. Died 23 November 1968, aged 55. Graduate of University of California Medical School, Berkeley-San Francisco, 1940. Licensed in California in 1940. Doctor Friedman was a member of the Alameda-Contra Costa Medical Association.

◆

Gardner, Irvin B., Burlingame. Died 8 November 1968 in New Delhi, India, of heart disease, aged 56. Graduate of Baylor University College of Medicine, Houston, 1937. Licensed in California in 1945. Doctor Gardner was a member of the San Mateo County Medical Society.

◆

Gewertz, Louis Leonard, Firebaugh. Died 18 November 1968 in Los Angeles of cardiac arrest following operation for carcinoma of the stomach and pancreas, aged 70. Graduate of St. Louis University School of Medicine, St. Louis, Mo., 1923. Licensed in California in 1923. Doctor Gewertz was a member of the Fresno County Medical Society.

◆

Jewett, Russell A., Beverly Hills. Died 1 June 1968 of myocardial infarction, aged 84. Graduate of Western Reserve University School of Medicine, Cleveland, 1907. Licensed in California in 1917. Doctor Jewett was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

◆

Jones, Robert Alton, Long Beach. Died 4 November 1968 in Long Beach of respiratory and circulatory failure, aged 84. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1915. Licensed in California in 1915. Doctor Jones was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

◆

Kassel, Maxwell S., North Hollywood. Died 22 November 1968 in North Hollywood of coronary artery disease, aged 54. Graduate of University of California Medical School, Berkeley-San Francisco, 1940. Licensed in California in 1940. Doctor Kassel was a member of the Los Angeles County Medical Association.

◆

Levine, Benjamin, Los Angeles. Died 29 November 1968 in Los Angeles of heart disease, aged 73. Graduate of Detroit College of Medicine and Surgery, 1921. Licensed in California in 1926. Doctor Levine was a member of the Los Angeles County Medical Association.

Lowry, M. Lester, Beverly Hills. Died 1 November 1968 in Los Angeles of cardiorespiratory failure, aged 71. Graduate of Washington University School of Medicine, St. Louis, 1924. Licensed in California in 1924. Doctor Lowry was a member of the Los Angeles County Medical Association.

⁂

Nelson, Clarence Henry, Los Angeles. Died 19 November 1968 in Los Angeles of myocardial infarction, aged 66. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1929. Licensed in California in 1929. Doctor Nelson was a member of the Los Angeles County Medical Association.

⁂

Padgett, Vernon Wallace, Grass Valley. Died 27 October 1968 in Grass Valley, aged 64. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1933. Licensed in California in 1933. Doctor Padgett was a member of the Placer-Nevada County Medical Society.

⁂

Paxton, John Richard, Glendale. Died 2 November 1968 in Glendale of cerebral hemorrhage, aged 61. Graduate of University of Southern California School of Medicine, Los Angeles, 1936. Licensed in California in 1936. Doctor Paxton was a member of the Los Angeles County Medical Association.

⁂

Pressburger, Erich, San Francisco. Died 9 November 1968 in San Francisco, aged 71. Graduate of Medizinische Fakultät der Universität, Wein, Austria, 1924. Licensed in California in 1939. Doctor Pressburger was a member of the San Francisco Medical Society.

⁂

Rickenberg, Robert Edwin, Los Angeles. Died 29 November 1968 in Los Angeles of carcinoma, aged 53. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1942. Licensed in California in 1942. Doctor Rickenberg was a member of the Los Angeles County Medical Association.

⁂

Severy, Wendell L., Los Angeles. Died 6 November 1968 in Santa Monica of heart disease, aged 49. Graduate of Columbia University College of Physicians and Surgeons, New York City, 1942. Licensed in California in 1947. Doctor Severy was a member of the Los Angeles County Medical Association.

⁂

Sherry, Leroy B., Pasadena. Died 23 October 1968, aged 81. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1914. Licensed in California in 1919. Doctor Sherry was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

⁂

Stehr, Vernon C., Oakland. Died 9 November 1968 in Piedmont, aged 55. Graduate of University of Wisconsin Medical School, Madison, 1937. Licensed in California in 1938. Doctor Stehr was a member of the Alameda-Contra Costa Medical Association.

Talbot, Donald B., Burlingame. Died 11 November 1968 in San Jose, aged 41. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1955. Licensed in California in 1955. Doctor Talbot was a member of the San Mateo County Medical Society.

⁂

Tattersall, Kenneth Lysander, Oakland. Died 10 November 1968 in Oakland, aged 68. Graduate of University of California Medical School, Berkeley-San Francisco, 1927. Licensed in California in 1927. Doctor Tattersall was a member of the Alameda-Contra Costa Medical Association.

⁂

Thelen, Ernest, San Diego. Died 11 November 1968, aged 83. Graduate of Creighton University School of Medicine, Omaha, 1907. Licensed in California in 1924. Doctor Thelen was a retired member of the San Diego County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

⁂

Thomas, Gilbert Joshua, San Clemente. Died 27 November 1968 in South Laguna of cardiac arrest, aged 84. Graduate of Northwestern University Medical School, Chicago, 1908. Licensed in California in 1943. Doctor Thomas was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

⁂

Todd, Lois Pendleton, Palo Alto. Died 11 November 1968 in Stanford, aged 74. Graduate of University of California Medical School, Berkeley-San Francisco, 1920. Licensed in California in 1920. Doctor Todd was a retired member of the Santa Clara County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

⁂

Wills, Clarence A., Lafayette. Died 22 October 1968 in Walnut Creek of cardiac insufficiency, aged 89. Graduate of University of California Medical School, Berkeley-San Francisco, 1903. Licensed in California in 1903. Doctor Wills was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

⁂

Wilson, Harry H., South Pasadena. Died 4 December 1968 in Pasadena of terminal bronchopneumonia and Hodgkin's disease, aged 76. Graduate of University of Illinois College of Medicine, Chicago, 1916. Licensed in California in 1917. Doctor Wilson was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

He was also a past president of the California Medical Association and a past president of the Los Angeles County Medical Association.

⁂

Zak, Richard A., Montebello. Died 24 November 1968 in Montebello of myocardial infarction, aged 50. Graduate of University of Illinois College of Medicine, Chicago, 1944. Licensed in California in 1945. Doctor Zak was a member of the Los Angeles County Medical Association.

1969 ANNUAL SCIENTIFIC ASSEMBLY

OF THE CALIFORNIA MEDICAL ASSOCIATION

Ambassador Hotel
Los Angeles, March 15-19

Detailed Program Follows Page 106

Three general meetings focus on:

RECOGNITION AND TREATMENT

- **STROKE**
- **NEONATAL AND CONGENITAL DISEASES**
- **METABOLIC DISEASES**

RENOWNED SPEAKERS ARE:

ROBERT A. ALDRICH, M.D.
Professor and Head
Division of Human Ecology
Department of Pediatrics
School of Medicine
Director, Health Resources Study Center
University of Washington

ROBERT D. BLOODWELL, M.D.
Chief of Pediatric Surgery Section
Department of Surgery
Assistant Professor of Surgery
Baylor University College of Medicine

BARTON CHILDS, M.D.
Professor of Pediatrics
Johns Hopkins University
School of Medicine

CLARK H. MILLIKAN, M.D.
Senior Consultant
Department of Neurology
Mayo Clinic
Professor of Neurology
Mayo Graduate School of Medicine
(University of Minnesota)

JOSEPH E. RALL, M.D., Ph.D.
Director of Intramural Research
National Institute of Arthritis and Metabolic Diseases
National Institutes of Health

EIGHTEEN SCIENTIFIC SECTION PROGRAMS ON A VARIETY OF TOPICS

Special Conferences Include:

Self-Inflicted Drug Overdose
Family Life Education
AMA Conference on Nutrition
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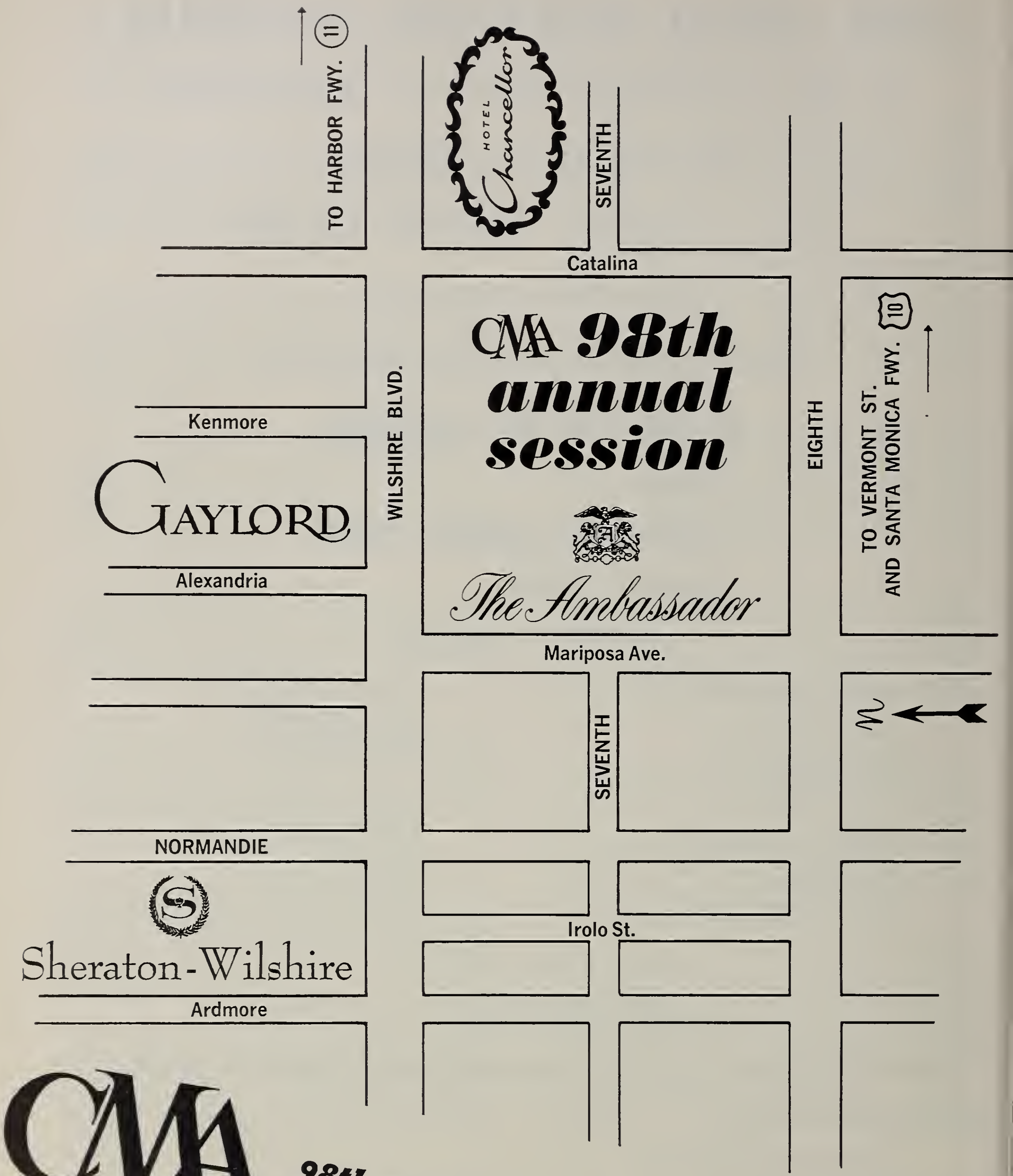
PLUS OUTSTANDING SCIENTIFIC AND TECHNICAL EXHIBITS


TO HARBOR FWY. 11
HOTEL Chancellor
SEVENTH
Catalina
CMA 98th annual session
The Ambassador
WILSHIRE BLVD.
EIGHTH
TO VERMONT ST. AND SANTA MONICA FWY. 10
Kenmore
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application for HOTEL ACCOMMODATIONS

NINETY-EIGHTH *Annual Session*

CALIFORNIA MEDICAL ASSOCIATION • MARCH 15-19, 1969
AMBASSADOR HOTEL, LOS ANGELES

House of Delegates Opening Session, Ambassador Hotel, Saturday evening, March 15;
Scientific Sessions, Ambassador Hotel, begin Sunday morning, March 16.

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1. Fill in the form below *completely* for room accommodations at the CMA's 1969 Annual Session. There is only a limited number of rooms available. Your choice of accommodations will be better if your request is for rooms to be occupied by two or more persons.
2. Your reservation request should include the definite date and hour of your arrival and departure.
3. All reservations must be made through the CMA Housing Bureau, Ambassador Hotel, 3400 Wilshire Boulevard, Los Angeles 90005 by *February 17, 1969.*

	Single	Double and Twin	Suites
AMBASSADOR HOTEL 3400 Wilshire Boulevard	$14-16	$18-22	$45-70
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Ambassador Hotel, 3400 Wilshire Boulevard, Los Angeles 90005

Please reserve the following accommodations for the CMA's 1969 Annual Session in Los Angeles, March 15-19.

Single Bedroom $.................. Twin-Bedded $.................. Double Bed $.................. Suite $..................

First Choice Hotel.................................... Second .... Third....................................

Arrival (date)...................... Hour.................. a.m. p.m. Departure (date)...................... Hour.................. a.m. p.m.

THE NAME AND ADDRESS OF EACH HOTEL GUEST MUST BE LISTED. Include names and addresses of *each* person in a double or twin-bedded room, and names and addresses of *all other persons* for whom you are requesting reservations.

Your Name: .... Officer?........ Delegate?........ Alternate?........ Speaker?........

Address: .... County ....

City and State.. Zip Code..................

GUESTS' NAMES AND ADDRESSES:

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CMA REGIONAL POSTGRADUATE INSTITUTE
FOR WEST COAST COUNTIES

Hyatt House Hotel, Monterey
March 6-7, 1969

program theme

Medical and Surgical Aspects of Acute Care

presented cooperatively by

West Coast Counties Medical Societies
Stanford University School of Medicine
California Medical Association

host: Monterey County Medical Society
Regional Chairman: William J. Kennedy, M.D.

institute fee: $20.00. For additional information contact:
Continuing Medical Education,
California Medical Association
693 Sutter Street, San Francisco 94102

All California Medical Association members and their families are cordially invited to attend.

WOMAN'S AUXILIARY

to the California Medical Association

Health Careers

OPPORTUNITY IS KNOCKING at the door; not just knocking but banging; banging to the youth of our nation to join the medical team. With Medi-Cal in effect and the enormous population growth of our state, someone must come forth and interest the students in Health Careers. This demand has become the prime objective of the 49 medical auxiliaries in California.

Health Careers has always been one of the auxiliaries' projects, but with the knowledge that we need 10 percent of all high school graduating seniors in the health field, our efforts for recruitment have become even more concentrated. Our motto is *Action* and we are increasingly involving not only our medical societies and auxiliaries but also the community, the hospital, the news media, the schools and the departments of public instruction as well as students and parents. We have also accepted the opportunity to help the Health Manpower Council in making surveys of the needs of each health field in our particular community, and of the student supply and what refresher courses are offered.

We have felt it most important to begin with the schools by sponsoring Health Career Clubs in the high schools. At present we have 187 Career Clubs and 32 Future Nurse Clubs in the state, and their object is to interest and inform boys and girls about the opportunities open to them in the field of health care and to broaden their knowledge of their own communities' medical facilities and needs. This is accomplished by the showing of specialized professional films and organizing field trips to hospitals, schools of nursing, schools for the retarded and handicapped, physical therapy clinics, pharmacy prescription laboratories and many others. Spending a day in the office of a physician of their choice has proven more than satisfactory, not only to the student but also to the physician, as both have become aware of each other's need. In some of the schools that do not have clubs, the auxiliary members go to the schools and set up a booth once a month (with permission of the school). There they pass out printed material and answer students' questions concerning health careers.

We feel that keeping the school councilors informed about the health field is very necessary. Thus we have had a Quick Reference Chart printed, listing 26 health careers, the education necessary, schools that are available in California, the expected income and what scholarships are available. We are now engaged in the process of getting one of these charts into every junior high school and high school in the state.

Another project that is growing every year and has a far-reaching effect is the Health Career Day or Health Fair. Last year 27 counties participated in this activity; some were of one day's duration; others went on as long as five days. Some were for just high school students and others were open to the public. Attendance ranged from 400 to 25,000. This media is one of the best means of disseminating the health career story because it encompasses many ways of communication. There are panel discussions, hospital tours, movies, displays and contact with people who work in all specific fields of medicine. Also, printed material is available to everyone.

What we have done for health career recruitment is cause for some feeling of pride, but we are not satisfied. California is called the progressive state and we have become a progressive auxiliary. We will continue to improve our old programs and we will begin new ones. Last year, almost $75,000 was given in scholarships, most of it going for nursing. Now we realize that we must make our scholarships available to all allied fields of medicine. Not only will we continue with the "candy striper" programs, but we hope to promote a program for boys in the hospitals. We intend to start refresher courses for inactive and retired nurses or to encourage hospitals that have discontinued such courses to begin anew. We also plan to advance health career education at the junior high school level and to continue it through the colleges and into the home, giving the parents the incentive and knowledge to guide their children toward a Health Career.

We know we have started a spark. As we become better informed and understand all the needs in the health field, we hope to fan it into full blaze.

MRS. HARLEY GREAVES
Health Careers Chairman

Presidents' Reception and Dinner

C.M.A. and Woman's Auxiliary

Ambassador Hotel, Los Angeles — Cocoanut Grove — March 16, 1969

RESERVE A PLACE

You must have tickets to attend. Tables of various sizes are available—four, six, eight, ten and twelve persons. An effort will be made to assign your party to the size table best suited to it. Tables will be filled. To reserve tickets, fill out the coupon and send your check.

- -

California Medical Association
3345 Wilshire Boulevard
Los Angeles, California 90005

Please reserve ____________ places for me for the Presidents' Dinner. Enclosed is my check for __________ ($15 per person). I understand refunds will not be made after February 21.

Name: ______________________________

Address: ______________________________

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PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H.
Director, State Department of Public Health

How Much Is Clean Air Worth?

One of California's great natural resources is going up in smoke — fresh air. About 85 percent of Californians live in counties with community-wide pollution problems caused by contaminants from automobiles, industrial processes, agriculture, waste disposal, aircraft and domestic activity. Rural communities, too, suffer from smoke, dust and odors from agricultural and industrial operations and waste disposal. Even on the western slopes of the Sierras, trees show signs of pollution.

Polluted air contributes to or exacerbates diseases of the respiratory system, including emphysema, chronic bronchitis, asthma and, possibly, lung cancer. Air pollution costs agriculture more than 200 million dollars a year. It damages timber, buildings, ornamental plants and the cut flower industry. It reduces visibility and produces offensive odors.

In response to this challenge, the Mulford-Carrell Act, passed in 1967, provided a focal point for air pollution functions in the state in a new Air Resources Board (ARB) which assumed all of the functions of the Motor Vehicle Pollution Board and many of those of the State Department of Public Health. The ARB was also given additional authority and responsibility not previously held by any state agency.

The State Health Department assumed air pollution control responsibilities by legislative mandate in 1955. Under the 1967 law, the department performs the following functions, some required by statute, others by interagency agreement with the ARB:

- Recommends division of the state into air basins separated from each other by natural barriers to massive air exchange, and to each of which appropriate air standards can be applied. The State Health Department advised division of California into 11 air basins and the ARB adopted these recommendations on 20 November 1968.
- Recommends standards of ambient air quality, reflecting the relationship between intensity and composition of air pollution and health effects.
- Recommends standards of ambient air quality for each of the basins, considering not only public health but the effects of pollution on the senses, esthetic values, interference with visibility and effects on the economy.
- Monitors air pollutants with a network of air quality surveillance stations and makes an inventory of emission sources throughout the state.
- Conducts laboratory investigations and epidemiological surveillance of California's populations to evaluate the effects of air pollution on human, plant and animal life; and studies the chemical factors responsible for pollution.
- Reviews rules and regulations of local and regional authorities to assure that provisions are made to control emission from non-vehicular sources and to achieve air quality standards set by the ARB in the area.

Although the Federal government has preempted the right to set motor vehicle emission standards, California, the only state which already had such standards at the time, is permitted to establish its own, subject to certain findings of need and attainability by the Federal Government. In 1968, state legislation was adopted which provides for increasingly stringent control of motor vehicle pollution over the next several years.

Local and regional authorities in California are responsible for controlling non-vehicular sources of air pollution in their own areas to meet state air quality standards. They may also set standards more stringent than those of the state. The state may enforce its air quality standards, as related to non-vehicular pollution sources, only after local authorities demonstrate that they cannot or will not do so.

In controlling and preventing air pollution, Californians will sometimes have to choose between conflicting goals. Health should certainly rank highest among such objectives, but relatively how important is the preservation of esthetic values, and how much agricultural damage is tolerable?

How much is a community willing to pay to clean up dirty skies and bad smells caused by industrial or agricultural activity which provides steady employment and a healthy economy? And what are the rights of a neighboring community to freedom from pollution?

These are a few of the questions to which Californians must seek answers in the years to come. Almost all air pollution can be controlled, but sometimes the cost is high.

Bridge the Generation Gap

REACH OUT TO YOUNG MEDICINE

Here is a good means of expressing your well wishes in a practical and comradely way to the young people who are the future of your profession.

For only $8 you can send a subscription to CALIFORNIA MEDICINE to a medical student—either to one you know, or, if you wish, to one that we will pick by lot from a list of the students in medical schools in California.

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EDUCATION NOTICES

Meetings and Courses

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of the dates of continuing education programs and the meetings of various medical organizations in California is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102; or phone: (415) 776-9400, extension 241.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Postgraduate Course Information

CMA:	**California Medical Association** For information contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. (415) 776-9400, ext. 240.
LLU:	**Loma Linda University** For information contact: John E. Peterson, M.D., Associate Dean for Research Affairs, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.
PMC:	**Pacific Medical Center** For information contact: Arthur Selzer, M.D., Chairman, Education Committee, Pacific Medical Center, Clay and Webster Streets, San Francisco 94115. (415) 931-8000.
STAN:	**Stanford University** For information contact: Thomas A. Gonda, M.D., Associate Dean, Stanford University School of Medicine, 300 Pasteur Drive, Palo Alto 94304. (415) 321-1200, ext. 5940.
UCD:	**University of California, Davis** For information contact: Charles J. Tupper, M.D., Dean, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0333.
UCI	**University of California — California College of Medicine, Irvine** For information contact: Robert Combs, M.D., Associate Dean, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5221.
UCLA:	**University of California, Los Angeles** For information contact: Donald Brayton, M.D., Associate Dean and Head, Continuing Education in Medicine and the Health Sciences, 15-39 Rehabilitation Center, UCLA Center for the Health Sciences, Los Angeles 90024. (213) 825-6756.
UCSD:	**University of California, San Diego** For information contact: Clifford Grobstein, Ph.D., Dean, University of California, San Diego, School of Medicine, La Jolla 92038. (714) 453-2000.
UCSF:	**University of California, San Francisco** For information contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, Health Sciences, University of California Medical Center, San Francisco 94122. (415) 666-1692.
USC:	**University of Southern California** For information contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 225-1511, ext. 203.

FEBRUARY

February 1—**Cancer.** PMC. Saturday.

February 1-2—**Pediatric Neurology.** UCSF at Children's Hospital and Adult Medical Center, San Francisco. Saturday-Sunday.

February 1-2 — **Seminar in Pediatric Urology.** Children's Hospital of Los Angeles. Saturday-Sunday. $65. Contact: H. H. Edelbrock, M.D., Seminar Director, Children's Hospital of Los Angeles, 6753 Hollywood Boulevard, Suite 706, Los Angeles 90028.

February 1-2—**Midwinter Radiological Conference.** International Hotel, Los Angeles. Saturday-Sunday. 14 hours. $30. Contact: Cal Williams, M.D., 15107 Van Owen, Van Nuys 91401.

February 1-2—**Trauma.** UCSF at Mary's Help Hospital, Daly City. Saturday-Sunday.

February 1-2—**Role of Medicine in Aviation Safety.** Sir Francis Drake, San Francisco. Saturday-Sunday. $10. Contact: CMA.

February 3 - March 10—**Postgraduate Course for Physicians.** John Muir Memorial Hospital, Walnut Creek. Monday evenings. $15. Contact: Loyse C. Casebolt, Executive Director, Contra Costa County Heart Association, P.O. Box 212, Walnut Creek.

February 4—**Low-Beer Memorial Lecture in Radiation Therapy.** Medical Sciences Auditorium, University of California Medical Center, San Francisco. Tuesday. Contact: Louise Sessions, Administrative Assistant, Section of Therapeutic Radiology, University of California Hospitals, San Francisco 94122.

February 4-April 22—**Bedside Cardiology.** USC. Tuesdays.

February 6-April 24—**Neuroradiology.** USC at LAC-USC Medical Center. Thursdays.

February 6-8—**Pediatric Ophthalmology.** UCSF at St. Francis Hotel, San Francisco. Thursday-Saturday.

February 8—**Coronary Artery Disease: Recent Trends in Diagnosis and Treatment.** PMC. Saturday. $35.

February 8-9—**Financial Tax and Investment Planning.** UCLA. Saturday-Sunday.

February 8-9—**Drugs: Psychedelic and Narcotic.** UCSF at Mendocino State Hospital, Talmage. Saturday-Sunday.

February 8-9 — **Obstetrical and Gynecological Forum.** Beverly Hilton Hotel, Beverly Hills. Saturday-Sunday. $30; $10, residents and interns. Contact: Los Angeles Obstetrical and Gynecological Society, 5410 Wilshire Boulevard, Los Angeles 90036.

February 10-14 — **Course for Physicians in General Practice.** UCSF at Mount Zion Hospital, San Francisco. Monday-Friday.

February 13—**Infections in the Newborn.** Los Angeles. Thursday. Contact: Mrs. Eve Black, Executive Secretary, Los Angeles Pediatric Society, P.O. Box 2022, Inglewood 90305.

February 14—**Urinary Infections: The Portal of Entry.** St. Mary's Long Beach Hospital. Friday. Contact: C. C. Calescibetta, M.D., Director of Medical Education, St. Mary's Long Beach Hospital, 509 East 10th Street, Long Beach 90813.

February 14-15—**Hand Injuries.** PMC. Friday-Saturday.

February 14-15—**Regional Meeting, Northern California and Nevada American College of Physicians.** San Francisco. Friday-Saturday. Contact: John R. Gamble, M.D., Governor, Northern California and Nevada Region, ACP, 655 Sutter Street, San Francisco 94102.

February 15 — **Ophthalmology and Dermatology.** UCSF. Saturday.

February 15-16—**Pediatric Neurology.** UCLA. Saturday-Sunday.

February 15-16—**Symposium on Arthritis.** USC. Saturday-Sunday.

February 16-20—**LLU Alumni Postgraduate Convention.** Loma Linda Medical Center and Ambassador Hotel, Los Angeles. Sunday-Thursday. $50 or $15/3-hour course. Contact: Samuel H. Fritz, M.D., General Chairman, 1832 Michigan, Los Angeles 90033.

February 17-March 12 — **Sacramento Valley Circuit Courses.** California Medical Association in cooperation with UCD and Sacramento Valley Counties Medical Societies. Mt. Shasta, Chico, Auburn. Mondays, Tuesdays, Wednesdays. 12 hours. $20. Contact: CMA.

February 17 - May 12 — **Emotional Family Problems within a Medical Practice.** USC Division of Postgraduate Psychiatry at Daniel Freeman Hospital, Westchester-Inglewood. Monday. $35. Contact: Ronald A. Markman, M.D., Assistant Director, USC Division of Postgraduate Psychiatry. (213) 225-1511, extension 336.

February 18-April 22—**Teaching Clinics in Psychiatry.** UCLA. Tuesdays.

February 19—**Medical Practice in Haiti.** Agnews State Hospital, San Jose. Wednesday. Contact: J. Elizabeth Jeffress, M.D., Chief of Professional Education, Agnews State Hospital, San Jose 95114.

February 19-20—**Symposium on Shock.** USC at Statler Hilton Hotel, Los Angeles. Wednesday-Thursday.

February 21-22—**Regional Meeting, Southern California American College of Physicians.** Santa Barbara. Friday-Saturday. Contact: W. Philip Corr, M.D., Governor, Southern California ACP, 1220 Arlington Avenue, Riverside.

February 25 - May 13—**Psychiatric Principles in Medical Practice.** USC Division of Postgraduate Psychiatry at Santa Clara Valley Medical Center. Tuesdays (7-9 p.m.). $35. Contact: Ronald A. Markman, M.D., Assistant Director, Division of Postgraduate Psychiatry, USC. (213) 225-1511, extension 336.

February 25 - May 20—**Surgical Emergencies—Acutely Ill Patient.** USC. Tuesdays.

February 26-28 — **Neuroelectric Conference.** Jack Tar Hotel, San Francisco. Wednesday-Friday. Contact: David V. Reynolds, Ph.D., Stanford Research Institute, 333 Ravenswood Avenue, Building 18, Menlo Park 94025.

February 26-March 2—**Surgery.** UCLA in Palm Springs. Wednesday-Sunday.

February 28—**The Management of Chronic Renal Failure.** St. Mary's Long Beach Hospital. Friday. Contact: C. C. Calescibetta, M.D., Director of Medical Education, St. Mary's Long Beach Hospital, 509 East 10th Street, Long Beach 90813.

February 28-March 1—**Congenital and Hereditary Defects of the Musculo-Skeletal System.** UCSF. Friday-Saturday.

February 28-March 1 — **Therapy in the Ambulatory Pediatric Patient.** Sacramento Inn. Friday-Saturday. Contact: J. Garland Stroup, M.D., Program Chairman, Sacramento Pediatric Society, 2628 El Camino Avenue, Sacramento 95821.

MARCH

March 1-2—**NIMH Program.** UCSF at Herrick Memorial Hospital, Oakland. Saturday-Sunday.

March 1-2—**Psychiatry for General Practitioners,** UCSF at Mendocino State Hospital, Talmage. Saturday-Sunday.

March 1-2—**Computers—Horizons in Biology.** UCSF. Saturday-Sunday.

March 2-5—**Controversial Areas in Gastroenterology.** UCLA in Palm Springs. Sunday-Wednesday.

March 4-8—**Diagnostic Radiology.** UCSF. Tuesday-Saturday. $30/day; $125, entire course.

March 4 - May 20—**Psychiatric Principles in Medical Practice.** USC Division of Postgraduate Psychiatry at Santa Clara Valley Medical Center, San Jose. Tuesdays. $35. 24 hours. Contact: Ronald A. Markman, M.D., Assistant Director, Division of Postgraduate Psychiatry, USC. (213) 225-1211, extension 336.

March 5 - May 21—**Psychiatric Principles in Medical Practice.** USC Postgraduate Psychiatry Division at Upland-Ontario. Wednesdays. $35. 24 hours. Contact: Ronald A. Markman, M.D., Assistant Director, Postgraduate Psychiatry Division, USC. (213) 225-1511, extension 336.

March 5-June 11—**Nuclear Medicine.** UCSF. Wednesdays.

March 6-7 — **WEST COAST COUNTIES — Regional Postgraduate Institute. California Medical Association in cooperation with Stanford and West Coast Counties Medical Societies.** Hyatt House, Monterey. Thursday-Saturday. 12 hours. $20. Contact: CMA.

March 6-8—**Nuclear Medicine.** UCSF. Thursday-Saturday.

March 7-8 — **Clinical Neurology: Recent Advances.** UCSF. Friday-Saturday.

March 7-12—**American Association of Pathologists and Bacteriologists.** Hilton Hotel, San Francisco. Friday-Wednesday. Contact: J. L. Orbison, Executive Secretary, American Association of Pathologists and Bacteriologists, University of Rochester, Rochester, New York 14620.

March 8—**Auscultation of the Heart.** PMC. Saturday.

March 8-9—**Children's Hospital Program II.** UCSF at Children's Hospital and Adult Medical Center, San Francisco. Saturday-Sunday.

March 9-11—**Videotape Self Observation.** UCLA in Palm Springs. Sunday-Tuesday.

March 10-21 — **Workshop in Mental Retardation.** UCLA. 10 days.

March 11-15—**Pathologic Physiology and Anatomy of the Platelet.** International Academy of Pathology at the Hilton Hotel, San Francisco. Tuesday-Saturday. Contact: F. K. Mostofi, M.D., Office of Secretary-Treasurer, Armed Forces Institute of Pathology, Washington, D.C. 20305.

March 11-15—**Diagnostic Radiology.** UCSF. Tuesday-Saturday.

March 14-15—**Medical Aspects of Well Being—Death and Dying.** UCSF. Friday-Saturday.

March 15—**Cervical Spondylosis.** PMC. Saturday.

March 15-16—**Psychiatric Program.** UCSF at Napa State Hospital, Imola. Saturday-Sunday.

March 15-16—**Techniques of Surgery of the Shoulder.** UCLA. Saturday-Sunday.

March 15-19 — **CALIFORNIA MEDICAL ASSOCIATION — Annual Scientific Assembly.** Ambassador Hotel, Los Angeles. Saturday-Wednesday. Contact: CMA.

March 19—**A Psychiatrist in Chinatown.** Agnews State Hospital, San Jose. Wednesday. Contact: J. Elizabeth Jeffress, M.D., Chief of Professional Education, Agnews State Hospital, San Jose 95114.

March 19—**San Francisco Neurosurgical Society.** Oak Knoll Naval Hospital. Wednesday evening, 6 p.m. Contact: Burton L. Wise, M.D., Room U-120, UC Medical Center, San Francisco 94122. (415) 666-1677.

March 21-23 — **Children with Learning Disorders.** UCSF. Friday-Sunday.

March 21-23—**New Concepts in the Diagnosis and Management of Pump and Electrical Failure of the Heart.** Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: William D. Nelligan, Executive Director, American College of Cardiology, 9650 Rockville Pike, Rockville, Maryland 20014.

March 22—**American Society of Clinical Oncology.** Hilton Hotel, San Francisco. Saturday. Contact: Mary E. Sears, M.D., Treasurer, American Society of Clinical Oncology, M. D. Anderson Hospital, Houston, Texas 77025.

March 22-23—**Postgraduate Assembly in Anesthesiology.** Statler Hilton Hotel, Los Angeles. Saturday-Sunday. Contact: David D. Cohen, M.D., Chairman, Postgraduate Assembly, Los Angeles County Society of Anesthesiologists, 18025 Parthenia Street, Northridge.

March 23-25 — **American Association for Cancer Research.** San Francisco. Sunday-Tuesday.

March 24-28 — **The Clinical Evaluation of Children with Learning Disorders.** UCSF. Monday-Friday. $100.

March 26-27—**Spring Symposium for Physicians Practicing General Medicine.** Statler Hilton Hotel, Los Angeles. Wednesday-Thursday. Contact: Los Angeles County Heart Association, 2405 West Eighth Street, Los Angeles 90057. (213) 385-4231.

March 26-27 — **Coronary Care and Rhythm Disturbances.** USC at Statler Hilton Hotel, Los Angeles. Wednesday-Thursday.

March 27-29—**Uveitis.** UCSF. Thursday-Saturday.

March 28—**Physicians' Symposium on Cardiovascular Diseases.** Hacienda Hotel, Fresno. Friday. Contact: Frances J. Cuthbertson, Executive Director, Central Valley Heart Association, 1759 Fulton Street, Fresno.

March 28-29—**Proctology.** UCSF. Friday-Saturday.

March 29—**Diseases of the Mouth.** UCLA. Saturday.

March 29 — **Clinical Conference in Ophthalmology.** PMC. Saturday.

March 29-30 — **Transcultural Psychiatry — Mexican-Americans.** UCSF at Agnews State Hospital, San Jose. Saturday-Sunday.

March 31-April 2—**American Association for Thoracic Surgery.** Fairmont Hotel, San Francisco. Monday-Wednesday. Contact: Thomas B. Ferguson, M.D., Executive Secretary, Suite 311, 7730 Carondelet Avenue, St. Louis, Missouri 63110.

APRIL

April 2—**Office Dermatology.** PMC. Wednesday.

April 2—**Clinical Uses of Isotopes.** PMC. Wednesday.

April 2 - June 4—**Group Methods.** UCSF at VA Hospital, San Francisco. Wednesdays.

April 5-6—**Pediatric Allergy.** PMC. Saturday-Sunday.

April 7-16 — **Cardiology for the Consultant.** Rancho Santa Fe Inn, San Diego. Two weeks. Contact: William D. Nelligan, Executive Director, American College of Cardiology, 9650 Rockville Pike, Rockville, Maryland 20014.

April 8-9—**American Association of Planned Parenthood Physicians.** St. Francis Hotel, San Francisco. Tuesday-Wednesday. Contact: Planned Parenthood, World Population, 515 Madison Avenue, New York 10022.

April 10-11—**General Surgery.** UCSF. Thursday-Friday.

April 10-12—**Current Concepts and Practice of Obstetrical Anesthesia.** UCSF. Thursday-Saturday. $75.

April 10-12 — **Western Electroencephalography Society.** Anaheim. Thursday-Saturday. Contact: E. E. Shev, M.D., 516 Sutter Street, Suite 812, San Francisco 94102.

April 11-12 — **Annual Symposium on Cardiovascular Diseases.** Sacramento-Yolo-Sierra Heart Association at Sacramento Inn, Sacramento. Friday-Saturday. Contact: Malcolm M. McHenry, M.D., Cardiopulmonary Laboratory, Sutter Memorial Hospital, 52nd and F Streets, Sacramento 95819. (916) 452-3271, extension 479.

April 11-12—**Vascular Surgery.** USC at Statler Hilton Hotel, Los Angeles. Friday-Saturday.

April 12—**Medical Emergencies.** UCLA. Saturday.

April 12-13 — **Postural Problems in Relation to the Foot.** UCSF. Saturday-Sunday.

April 12-13—**Psychiatry Program.** UCSF at Stockton State Hospital. Saturday-Sunday.

April 12-13—**Heart Conference.** RMP Area VI at Holiday Inn, Palm Springs. Saturday-Sunday. $10. Contact: John E. Peterson, M.D., Associate Dean for Research Affairs, Loma Linda University School of Medicine, Loma Linda 92354.

April 13—**Obstetrical Emergencies.** UCLA. Sunday.

April 13-17—**Pacific Coast Oto-Ophthalmological Society.** Hilton Hotel, San Francisco. Sunday-Thursday. Contact: Francis A. Sooy, M.D., Secretary-Treasurer, Department of Otolaryngology, UC Medical Center, San Francisco 94122.

April 16—**Working with the Chinese in San Francisco.** Agnews State Hospital, San Jose. Wednesday. Contact: J. Elizabeth Jeffress, M.D., Chief of Professional Education, Agnews State Hospital, San Jose 95114.

April 17-19—**Advances in Endocrinology and Metabolism.** UCSF. Thursday-Saturday.

April 17-18 — **Annual Meeting, California Thoracic Society.** El Cortez Hotel, San Diego. Thursday-Friday. Contact: William F. Roberts, Director, Public Relations Division, TB and Health Association of California, 424 Pendleton Way, Oakland 94621. (415) 636-1756.

April 18—**Neurological Evaluation.** PMC. Friday.

April 18 — **Spring Symposium in Heart Disease.** Orange. Friday. Contact: Janice Ayres, Orange County Heart Association, 1043 West 8th Street, Santa Ana 92703.

April 26-27—**Comparative Oncology.** UCSF. Saturday-Sunday.

April 27-29—**American Society of Maxillofacial Surgeons.** Fairmont Hotel, San Francisco. Sunday-Tuesday. Contact: Dicran Goulian, Jr., M.D., Secretary-Treasurer, 116 East 68th Street, New York 10021.

April 30 - May 3 — **American Association of Plastic Surgeons.** Fairmont Hotel, San Francisco. Wednesday-Saturday. Contact: Clarence W. Monroe, M.D., Secretary, 715 Lake Street, Oak Park, Illinois 60301.

REPAIR OF RECURRENT INGUINAL HERNIA

"The first thing you have to do in repairing a recurrent [inguinal] hernia is to take your time. I think the important thing is to actually identify your layers and do a proper job. Too many of us do procedures instead of fix the hernia. Sometimes you go in and you don't have to do a whole procedure. You notice that there is a little recurrence on the floor and it can be fixed, or there is a little recurrence around the inguinal ring and it can be fixed without taking the whole floor down. To take the whole floor down just because you say, 'Well, I always do a McVay' or 'I always do a Bassini' or 'I never do a Halsted' is ridiculous. Sometimes we repair these and when we finish we've done a procedure we can hardly describe. It really doesn't have anybody's name and it still works."

—ROBERT H. QUILLINAN, M.D., Sacramento
Extracted from *Audio-Digest Surgery*, Vol. 15, No. 20, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

News & Notes

LOS ANGELES

Dr. Elmer Anderson has been named medical director of the new Martin Luther King, Jr., Hospital, now under construction in Southeast Los Angeles, and **Dr. Mitchell W. Spellman** has been appointed dean of the Charles R. Drew Postgraduate Medical School which will be located in the hospital.

Dr. Anderson will continue in his present post as medical director of the county's John Wesley Hospital probably until shortly before the new structure is completed, in the fall of 1970.

The new hospital, which will have a capacity of 394 beds, is being built on a 30-acre site at 120th and Wilmington.

The Drew postgraduate school will provide educational and research facilities for interns and resident physicians. It will act in affiliation with the medical schools of the University of California at Los Angeles and the University of Southern California. The faculty of the postgraduate medical school will hold appointments either within the UCLA or the USC Schools of Medicine.

* * *

The University of Southern California School of Medicine's Pharmacology Department and its programs of teaching and research are to be expanded, and **Dr. Samuel P. Bessman,** formerly of the University of Maryland, has been named chairman of the department, Dean Roger O. Egeberg announced recently.

Specialized studies of how therapeutic agents work on known or assumed metabolic pathways of health and disease, an area which long has been of interest to Dr. Bessman, will be added to the department's research efforts. Research in pharmacology, which has been based on the physiology of heart muscle, will continue, Dr. Bessman said.

* * *

Dr. David Belais Friedman, Associate Professor of Pediatrics, USC School of Medicine, received the Ross Award in Education at the recent annual meeting of the Western Society for Pediatric Research in Denver. The award was conferred for "outstanding contributions to education in pediatrics."

* * *

The 18th annual **Obstetrical and Gynecological Forum,** sponsored by the Los Angeles Obstetrical and Gynecological Society, will be held at the Beverly Hilton Hotel, Beverly Hills, California, on Saturday and Sunday, February 8 and 9, 1969. Registration fee is $30, with a special fee of $10 for residents and interns. Further information may be obtained from the Los Angeles Obstetrical and Gynecological Society, 5410 Wilshire Boulevard, Los Angeles 90036.

* * *

The Los Angeles Radiological Society's 21st annual Midwinter Conference will be held February 1 and 2, 1969, at the International Hotel, Los Angeles International Airport.

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The Research Study Club of Los Angeles will hold its 38th annual mid-winter convention in ophthalmology and otolaryngology January 20 to 24, 1969, at the Statler Hilton Hotel, Los Angeles. Guest speakers will be Drs. John Tonkin, Sydney, Australia; Douglas Ranger, London; David W. Brewer, Syracuse, New York, and Joseph L. Goldman, New York City.

ORANGE

The appointment of **Dr. Thomas L. Nelson** as associate dean for academic affairs at the University of California, **Irvine-California College of Medicine,** has been announced by Dean Warren L. Bostick. In addition to his new administrative appointment, Dr. Nelson will continue as professor and chairman of the college's department of pediatrics, positions he has held since 1964.

SAN FRANCISCO

Dr. Julius H. Comroe, Jr., director of the University of California Cardiovascular Research Institute, San Francisco, recently received the American Heart Association's 1968 **Research Achievement Award.** The highest honor given to research scientists by the Heart Association, an illuminated scroll and a $1,000 honorarium were presented to him for "his original contributions to science during an illustrious career of more than 30 years."

The **International Academy of Pathology** will hold its 58th annual meeting March 11 to 15 in San Francisco. Features of the scientific program will be a symposium on Evaluation of Platelet and Megakaryocytic Function, Tuesday, 11 March, at 8:00 p.m.; a symposium on Correlation of Platelet Structure and Function, Wednesday, 12 March, at 8:00 p.m.; and a course on Pathological Physiology and Anatomy of the Platelet, Thursday, 13 March, beginning at 8:30 a.m.

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The sixth **Low-Beer Memorial Lecture** in radiation therapy will be held at the University of California Medical Center, San Francisco, on Tuesday, 4 February, at 8:00 p.m. **Dr. Juan A. del Regato**, medical director of the Penrose Cancer Hospital, Colorado Springs, and clinical professor of radiology, University of Colorado School of Medicine, will speak on "Radiation Therapy in the Conservative Management of Adenocarcinoma of the Prostate." The lecture will be held in the auditorium, Medical Sciences Building, and all physicians are invited to attend.

SAN MATEO

Dr. Marvin L. Auerback of San Mateo has been elected president of the California Society of Pediatric Cardiology for the year 1968-1969. He succeeds Dr. Sam Sapin, Panorama City. The newly elected vice president is **Dr. Arthur J. Moss**, Los Angeles, professor and chairman of the Department of Pediatrics of the University of California at Los Angeles School of Medicine. **Dr. Rodger Shepherd**, San Francisco, was elected secretary-treasurer.

SANTA BARBARA

Internists in Southern California will attend a regional meeting of the **American College of Physicians** in Santa Barbara, February 21 to 22. The session is one of 35 scientific-educational meetings the ACP sponsors in various parts of the United States and Canada during the academic year.

EPSOM SALTS FOR NOSEBLEED WITH HIGH BLOOD PRESSURE

"Whenever I have patients in the office who have a nosebleed and a blood pressure of 250 over 140, I give them 4 or 6 cc of 50 percent epsom salts (magnesium sulfate) intramuscularly. It's a good old-fashioned hypotensive, and in the correctly hit cases will drop blood pressure 40 or 50 points in three or four minutes and keep it down for about eight hours. That way, whatever treatment I use to stop the nosebleed will have a better chance of working."

—ELMER C. BRICCA, M.D., San Francisco

Extracted from *Audio-Digest Otorhinolaryngology*, Vol. 1, No. 3, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

BOOK REVIEWS

California Medicine does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

MANUAL OF ELECTROTHERAPY — Third Edition — Arthur L. Watkins, M.D., Assistant Clinical Professor of Medicine, Harvard Medical School; Chief of Physical Medicine, Massachusetts General Hospital. Lea & Febiger, 600 S. Washington Square, Philadelphia, Pa. (19106), 1968. 262 pages, $6.50.

This is the third edition of this manual of electrotherapy, which refers to all the electrical modalities which I used in physical therapy. This includes the use of radiant energy (infrared heating), ultraviolet, low voltage and low frequency currents, high frequency currents (diathermy) and ultrasound. The electrophysics, instrumentation, application, and a few indications are given for each modality. Brief mention is also made of electromyography. The book is well written, well illustrated, and quite concise in its descriptions. It is excellent in its elementary presentation.

In these days of emphasis on exercise and activities of daily training, as well as vocational training and rehabilitation, the physical therapy treatment of the patient with simple musculoskeletal disease has become so routine that few physicians understand its application and rationale. This book was designed for the student of physical therapy and for those physicians who wish to have a well-done introduction into the electrotherapy aspect of physical therapy.

S. Malvern Dorinson, M.D.

* * *

THE NEONATE WITH CONGENITAL HEART DISEASE — Richard D. Rowe, M.B., Ch.B., F.R.C.P. Edin., Professor of Pediatrics, The Johns Hopkins University School of Medicine; Director, Cardiac Clinic, Children's Medical and Surgical Center, The Johns Hopkins Hospital, Baltimore; and Ali Mehrizi, M.D., Assistant Professor of Pediatrics, The Johns Hopkins University School of Medicine; Children's Medical and Surgical Center, The Johns Hopkins Hospital, Baltimore. Volume V in the Series "Major Problems in Clinical Pediatrics," Alexander J. Schaffer, Consulting Editor. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1968. 445 pages, $12.50.

This is the fifth volume in a series entitled "Major Problems in Clinical Pediatrics," edited by Alexander J. Schaffer, the consulting editor for the W. B. Saunders Co., of Philadelphia, London and Toronto.

This is not the first book devoting itself entirely to the problem of the diagnosis and treatment of the newborn infant with congenital cardiac abnormalities, but it is the first one that really enters into the problem with some depth. Despite this, there are some disappointments. The first is that even though it states it is tailored to the needs of the pediatricians and the general practitioners, it takes a great deal of general knowledge of cardiac diagnosis for granted on the part of the reader beyond what is probably the average knowledge of those in the above mentioned specialties. Another deficit is the paucity of illustrations, particularly in the chapter on the electrocardiogram and vectorcardiogram, with no sample electrocardiograms of the various hypertrophies and only diagrams of the vectorcardiogram, with only a very scanty discussion of the electrocardiogram, one of the most important parameters so helpful in the differential diagnosis of congenital cardiac abnormalities.

The chapter on cardiac malformations with asplenia or polysplenia syndrome is most confusing, first in its attempt to pool together the cardiac malformations with both asplenia and polysplenia, and secondly in an absence of lucidity which leaves the reader somewhat perplexed as to the exact nature of the lesions which are characteristic of asplenia, as contrasted to the polysplenia syndrome.

Aside from these minor deficiencies, the book is an excellent source for those particularly interested in the differential diagnosis of cardiac abnormalities in the newborn period. Following the first part, which is a general introduction and approach to the infant with a cardiac abnormality, Part 2 describes in some detail the ten major cardiac malformations, Part 3—the less common disorders, Part 4—the rare anomalies, and Part 5—related problems, including a very brief chapter on the diagnosis and management of heart failure in the newborn. I would recommend this book as the best published thus far on the vitally important problem of the diagnosis and treatment of infants in that most critical period, the newborn.

Saul J. Robinson, M.D.

* * *

ORR'S OPERATIONS OF GENERAL SURGERY — Fourth Edition — George A. Higgins, M.D., F.A.C.S., Chief, Surgical Service, Veterans Administration Hospital, Washington, D.C.; Clinical Professor of Surgery, George Washington University School of Medicine; Clinical Professor of Surgery, Georgetown University School of Medicine. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1968. 861 pages, $27.00.

Since its first publication in 1944, Orr's textbook of the operations of general surgery has remained one of the best in which the step-wise method of presentation of operative procedures is used. The fourth edition of this work maintains the standards of quality set by the previous three.

A new printing format makes this text similar to other modern texts and improves its readability. This edition is shorter than the third by 155 pages and contains 41 fewer figures, yet there are 2,048 step-by-step illustrations of operative procedures, all of which are quite clear and of excellent quality. Comparison of the third and fourth editions reveals that the shortening of the latter is accomplished by the deletion of various procedures that are no longer particularly useful in the realm of modern surgery.

The scope of the work remains quite large, though the bulk of the material pertains to that which is still considered general surgery. Other areas covered include chapters on neurological, orthopedic, gynecological and genito-urinary procedures. The more common operations in each of these fields are presented quite thoroughly, complete with excellent illustrations.

For the most part, the content of the fourth edition is very much like that of the third. As one should expect, the chapter on cardiovascular surgery is completely new. This is the only chapter that has been essentialy rewritten. It is sufficiently complete for most who would be interested in this type of text, but understandably is too sketchy for the specialist in cardiovascular surgery. The chapters on gastrointestinal surgery are appropriately modernized. Examples are increased emphasis on colon and jejunal interposition procedures for esophageal replacement and the inclusion of the newer pancreatic procedures of Bowers and Peustow. The chapter on hernia now includes the operations of La Roque and Nyhus and several older operations are deleted. The section on genitourinary surgery now includes the Keeley procedure for undescended testicle, to the exclusion of the older Torek operation. Ureterosigmoidostomy is placed in proper perspective as a procedure of very little use and great potential danger and much detail is provided concerning the construction of the Bricker ileal bladder.

In general, this volume is considered to be an excellent and perhaps essential addition to the library of the general surgeon. It is an extremely useful and important work. However, in the opinion of this reviewer, the fourth edition does not contain a sufficient amount of new material to warrant its purchase at a price of $27.00, if one already owns a copy of the third edition which is in satisfactory condition.

Gordon H. Puryear, M.D.

* * *

THE PHARMACOLOGY OF INFLAMMATION—W. G. Spector, M.B., B.Chir. (Camb.), F.R.C.P., Professor of Pathology, St. Bartholomew's Hospital Medical College, London, and D. A. Willoughby, Ph.D. (Camb.), M.C.Path., Reader in Experimental Pathology, St. Bartholomew's Hospital Medical College, London, Quondam Fellow, St. John's College, Cambridge. Grune & Stratton, Inc., 381 Park Avenue South, New York City (10016), 1968. 123 pages, $5.00.

This volume is a review of the experimental evidence documenting the nature of the inflammatory reaction and the effects of specific substances on various aspects of the reaction. These substances include endogenous substances such as histamine and serotonin, polypeptides, and polypeptide-forming systems such as bradykinen and kallikrein, and anti-inflammatory drugs such as salicylates, antihistamines and indomethacin. There is a separate chapter on the testing of anti-inflammatory drugs. The text is lucid and is illustrated well with both graphical presentations of data and reproductions of electron micrographs. The work should be of interest to practitioners in the fields of dermatology, rheumatology, infectious disease, and allergy, as well as to persons engaged in studies of inflammatory disease at the laboratory level.

Alvin Davis, M.D.

* * *

PROPRIOCEPTIVE NEUROMUSCULAR FACILITATION — Patterns and Techniques—Second Edition—Margaret Knott, B.S., Coordinator of Patient Services, Kaiser Foundation Rehabilitation Center, Vallejo, California, and Dorothy E. Voss, B.Ed., Associate in Physical Therapy, Northwestern University Medical School, Chicago, Illinois. With illustrations by Helen Drew Hipshman and James B. Buckley; foreword by Sedgwick Mead, M.D. Hoeber Medical Division, Harper & Row, Publishers, 49 East 33rd Street, New York City (10016), 1968. 173 pages, $9.50.

The second edition of this book is much greater in scope than the first. The work declares its theory and purpose in an introduction.

In the remaining sections techniques are depicted by excellent illustrations and are clearly described. The sections on patterns and techniques of facilitation, stimulation of vital and related function, evaluation and treatment program and the reference tables contain essentially the same material as the 1956 edition, with some rearrangement and a minimum of rewriting.

Section 3, "Facilitation of Total Patterns" is new, and stresses the use of the developmental sequence. This section describes and illustrates mat, gait, wheelchair transfer and self-care activities. Three and a half pages of references and suggested reading comprise Section 6. In the first edition the lack of any references with only 11 items listed for suggested reading was a weakness.

Proprioceptive neuromuscular facilitation has been evolved as a more effective way in which treatment can be applied. In the foreword, Sedgwick Mead, M.D., Medical Director of the Kaiser Foundation and Rehabilitation Center states: "I have come to feel that it exceeds all other methods of therapeutic exercise in speed of improvement, economy of time and thoroughness of results."

This is the only book which presents graphically and in detail, these now well-accepted techniques of interest to physical therapists, and to rehabilitation-minded physicians throughout the world. The subject seems too complex to master by reading and practicing alone without supervision, but the book will be invaluable as a text for those who are being given orientation and training by experts. Later, the book can serve as a manual.

Lucile Eising, M.D.

California
Medicine

Diabetes Mellitus—Current Criteria For Laboratory Diagnosis

RALPH W. ALEXANDER, M.D., *San Francisco*

■ *Among the laboratory methods and test procedures used for the diagnosis of diabetes mellitus in clinical practice, the oral glucose tolerance test, if performed properly, remains the cornerstone in the definitive diagnosis of diabetes. The intravenous glucose tolerance or the tolbutamide response tests may be indicated especially when there is a question of proper oral carbohydrate assimilation. The value of the cortisone-glucose tolerance test is still in question. Insulin assays may be helpful in differentiating between the various types of diabetes. Accepted criteria for normal and abnormal values for all tests are tabulated.*

EMPHASIS IN THE field of diabetes is shifting to the earlier recognition and treatment to prevent long-term complications. Several studies have indicated that carbohydrate intolerance predisposes to degenerative vascular diseases.[1-3] Furthermore, these complications are seen as frequently in patients with overt diabetes treated with hypoglycemic agents as in the asymptomatic group often not treated.[4] Therefore, it is felt that an abnormality of glucose metabolism, however early, may actually facilitate the process of atherosclerosis.[5] One would hope that with treatment of even the mildest carbohydrate intolerance,[6,7] the premature appearance of degenerative vascular disease might be averted or delayed.

With early detection at a premium, it becomes important to select tests which are sensitive and whose results are reproducible. Unfortunately, diagnostic laboratory criteria have to be based on statistical norms rather than on an individually demonstrable defect. Therefore, the currently accepted criteria to be reviewed here must be interpreted with care. Nevertheless, one should accept objective laboratory evidence for diabetes mellitus promptly and initiate appropriate therapy. In a recent survey,[8] it was discovered that among people with typically diabetic blood sugar values, only 61 percent were diagnosed by the examining physician as having diabetes mellitus. Conversely, among patients classified as diabetic, most frequently on the basis of glycosuria, only 41 percent had laboratory evidence to substantiate the diagnosis. These figures suggest a lack of appreciation in the interpretation of diagnostic laboratory criteria.

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Submitted 2 Dec. 1968.

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TABLE 1.—*Urine Sugar Tests*

			Urine Sugar Content and Color Reaction						
Method	*Principle*	*Stability*	*Neg.*	*0.1%*	*0.25%*	*0.5%*	*0.75%*	*1.0%*	*2.0% or more*
Benedict's	Cu reduct.	Stable	Blue	Blue	Drk. grn.	Green	Grn. yel.	Yellow	Drk. red
Clinitest® tabs	Cu reduct.	Unstable	Blue	Blue	Drk. grn.	Olive	Grn. brn.	Tan	Orange
Clinistix®	Gluc. oxid.	Unstable	Pink	Lt. pur.	Gradually darker				Drk. pur.
Testape®	Gluc. oxid.	Unstable	Yellow	Lt. grn.	Gradually darker				Drk. grn.

Urine Sugar Determinations

Four methods commonly used are listed in Table 1. Benedict's solution and Clinitest® tablets determine any copper-reducing carbohydrate, and therefore are not as specific as Clinistix® and Testape,® which react only with glucose. Also, they are not as sensitive, starting color change at 0.25 percent glucose content as compared with 0.1 percent for the glucose oxidase methods. Of course, the more sensitive the method, the greater the number of false positives.

The main advantages of Benedict's solution are its low cost and stability. The other test materials deteriorate with time. The copper-reduction methods are easier to interpret quantitatively by the definite color changes with different glucose concentrations. With practice, however, the paper methods may give a fair quantitative approximation. Their simplicity is a great advantage. Although urine sugar tests are the least expensive and quickest of all methods, they are not reliable in detecting diabetes mellitus.[9] As many as 63 percent of elderly people with glycosuria are called diabetic, without an abnormality of the blood sugar test.[8] Conversely, many persons with early diabetes have negative tests for urine sugar and show abnormal elevation of blood sugar only temporarily after eating. These patients would be missed by a urine screening method.[9,10,11] The sensitivity may be increased by testing urine two or three hours after a meal.[11]

Tests Based on Blood Sugar Content

The common methods used for the determination of blood sugar are listed in Table 2. The well known Folin-Wu procedure requires a protein-free blood filtrate prepared with tungstic acid. This fails to remove other non-glucose copper-reducing substances, which are present in variable quantities. These are removed with the zinc sulfate precipitation of proteins used in the Somogyi-Nelson technique. The Folin-Wu method has been largely supplanted by one of the "true" blood sugar methods listed, which are all specific for glucose and have the same normal range.

The use of plasma has gained general acceptance lately for two reasons: (1) It is free of non-fermentable reducing substances (for example, lactose) and yields a true value for glucose, and (2) it may be easily adapted to automation. However, one must interpret the normal values differently from those of whole blood. They are usually 10 to 15 percent higher, since without cellular proteins and membranes there is more glucose present per milliliter. The Dextrostix® method, although specific for glucose, is subject to errors in color interpretation. It is done on capillary (arterial) blood, and values are usually about 20 mg per 100 ml higher than for venous blood in the fasting state, although the normal range is not very well defined. Hence, the Dextrostix® method is not as reliable for a screening procedure, but it is often used for this purpose because of its sim-

TABLE 2.—*Blood Sugar Tests*

		Normal Fasting Range mg/100 ml		
Method	*Principle*	*Whole Blood*	*Serum or Plasma*	*Remarks*
Non-Specific:				
Folin-Wu	Cu reduct.	80-120		Includes non-glucose reducing substances.
"True" blood sugars:				
a. Somogyi-Nelson	Cu reduct.	65-100	70-110	Done on venous blood.
b. Autoanalyzer	Fe reduct.		70-110	No glycolysis with serum or plasma.
c. Glucose Oxidase	Gluc. oxid.	65-100	70-110	
d. Dextrostix®	Gluc. oxid.	65-120 ?		Capillary (arterial) blood. Difficult to read exactly.

plicity.[12] Its greatest value lies in the rapid identification of diabetic coma or insulin reaction.

The values for blood glucose quoted in the following test descriptions are those obtained by a "true" blood sugar method performed on venous whole blood.

Screening Tests

Fasting Blood Glucose—The blood glucose is determined after an overnight fast. Only water is allowed since even coffee may influence the blood sugar content.[13] This is a poor screening test since it does not detect early mild diabetes in which intolerance is shown only after a sugar load. On the other hand, if the fasting blood glucose value is greater than 120 mg per 100 ml, glucose tolerance tests are usually unwarranted.

Two-Hour Postprandial Blood Glucose — This is the best available screening test used and is extremely reliable, if performed properly. No food except water is taken after dinner the night before. The next morning 100 gm of glucose dissolved in 250 to 500 ml of flavored water is ingested within 15 minutes, and a blood specimen is obtained two hours from the start of ingestion.* If the patient is unable to retain the glucose drink, a gelatin may be better tolerated† or a 100 gm carbohydrate breakfast can be taken instead. An example of such a meal is: 8 ounces of orange juice, one bowl of cooked or dry cereal with milk and one tablespoon of sugar, and two slices of bread or toast with jam or jelly. Coffee or tea are taken as desired. Cream, butter, ham, eggs or other such foods are avoided since fats may delay gastric transit time and thus carbohydrate absorption. The blood specimen is obtained two hours after beginning the breakfast, which should be eaten within 15 minutes. Values may be slightly lower than those obtained after taking a glucose drink.[14]

The normal value is less than 110 mg per 100 ml. If the results fall between 110 and 180 mg per 100 ml, a glucose tolerance test should be performed. If the result is greater than 180 mg per 100 ml, the diagnosis of diabetes is established and further testing is unnecessary.

Some physicians have used less than a 100 gm glucose challenge.[14]‡ It is not certain whether this will alter the criteria for the normal range. A one-hour postprandial value is also used in screening tests and is abnormal if greater than 170 mg per 100 ml. It is probably not as reliable, since the peak concentration may occur before one hour. Furthermore, many non-diabetic persons show high one-hour values due to rapid absorption (tachyalimentation) with normal two-hour values.

Definitive Tests

Standard Oral Glucose Tolerance Test — This test is the cornerstone for the identification of diabetes mellitus. Since it is time-consuming, relatively costly, and uncomfortable, it should be performed under ideal conditions to enhance its usefulness. Since omission of carbohydrate from the diet for only two days can lower glucose tolerance, sometimes called "starvation diabetes,"[15] it is most important to insure proper carbohydrate intake for three days before the test. This is easily achieved in persons with good nutritional status by including 150 gm of carbohydrate with their diet per day. To avoid misunderstanding, the patient can be told, for example, to include two slices of bread with each of his three daily meals for three days before the test. In cases of suspected malnutrition, this should be increased to 300 gm of carbohydrate per day. A delay in glucose tolerance sometimes seen after physical exercise is also prevented by such carbohydrate "priming."[15]

After an overnight fast, the first blood specimen is obtained. Following this, the subject drinks a 100 gm glucose solution as described in the previous section. If the body weight is less than 45 Kg (100 pounds) 1.75 gm of glucose per Kg ideal body weight is given instead. Further blood specimens are obtained at one, two and three hours after the glucose drink.

The criteria for interpretation are given in Table 3. The earliest stage of clinical diabetes mellitus is established when *both* one-hour and two-hour values are abnormal in the presence of a normal fasting blood sugar. This phenomenon is seen in the large asymptomatic group with relatively little glycosuria during a 24-hour period, often missed with improper detection methods. Abnormal values of the fasting or three-hour specimen *alone* make the diagnosis of diabetes. This represents a later stage of the disease when most diabetic patients are already symptomatic because of glycosuria and usually seek medical attention

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*Commercial liquid preparation containing 100 gm glucose—Dexade®, Dexicola®, Dextol®, Glucotol®, Koladex®, Pala-dex® (cost between $.60 to $1.00 per bottle).

†Commercial gelatin containing 100 gm glucose: Geladex® (cost $1.00 per serving).

‡Glucola® contains 75 gm of glucose.

TABLE 3.—*Oral Glucose Tolerance Test*

	Values in mg/100 ml					
	Fasting	*½ hour*	*1 hour*	*1½ hour*	*2 hour*	*3 hour*
Normal	< 100	< 160	< 160	< 135	< 110	< 100
Abnormal	110 or more	170 or more	170 or more	145 or more	120 or more	110 or more

Diabetes if: 1. Abnormal fasting or 3-hour value; or, 2. Abnormal peak and 2-hour value; or, 3. Abnormal 1½-hour value with abnormal peak and borderline 2-hour values or vice versa.

on their own. A half-hour value may be included and used instead of the one-hour value, in cases where the peak blood glucose concentration occurs earlier. A value at one and a half hours may be of help if either the peak or two-hour value is borderline.

Early abnormalities in glucose tolerance must be interpreted in the light of some other factors:

- Much has been written (well summarized in a recent reappraisal[16]) about the influence of age on the glucose tolerance test. Glucose tolerance decreases in a linear fashion after the third or fourth decade in population studies.[17,18] On the other hand, elderly subjects with such early glucose intolerance also show a decrease in blood insulin[19] or a prolonged secretion,[20] which is compatible with the increased incidence of diabetes in the elderly. Such carbohydrate intolerance, however, may not be related to genetic factors.[21] It is my opinion that — until more information becomes available — the criteria of glucose tolerance tests set forth in Table 3 should at present be used without regard to age.
- Normally there is no "sex difference" in glucose tolerance values. Many women of all ages, however, are taking various types of estrogenic preparations. Ovulation suppressants, for example, tend to decrease glucose tolerance.[22] Two independent studies show a diabetic curve in about 20 percent of women who were taking such preparations.[23,24] The action of estrogens is probably similar to that of glucocorticoids, which lower renal threshold for glucose[25] and interfere with glucose transport across the cell membrane.[26] Hence, such women may have temporary steroid diabetes but some may turn out to have subclinical (latent) diabetes mellitus[22] as identified with the cortisone-glucose tolerance test described below. The effect of pregnancy is the same. Mildly abnormal test results must therefore be interpreted with caution in such women, but certainly careful follow-up testing is warranted. If a patient is taking cyclic estrogens, glucose tolerance studies are more reliable if done at least three days after the last pill of a cycle has been taken.
- The action of insulin is antagonized by many other hormones.[26] Hence, excessive endogenous production of steroids, thyroxine, catecholamines or growth hormones, as well as exogenous sources of such hormones, must be considered when interpreting the tolerance test values.
- Among other drugs affecting carbohydrate tolerance, the thiazides are clinically the most important. The mechanism of the occasional hyperglycemic response is not clear, but these drugs may interfere with hepatic uptake of glucose[27] or with peripheral glucose utilization,[28] both of which may be related to potassium loss.[29] Other mechanisms which have been suggested are direct toxic effect on islet cells by thiazides[30] or hepatic glycogenolysis via epinephrine release.[31,32]

Intravenous Glucose Tolerance Test—The intravenous method is probably not as reliable as the oral method for the identification of the very early diabetic state. At present, the test is mainly used for persons who cannot tolerate the rapid oral glucose load, and vomit, or who have a history of gastrectomy or gastrointestinal disorders influencing intestinal absorption of glucose.

The patient is prepared as with the standard oral glucose tolerance test. After an overnight fast, 25 gm of glucose is injected as a 50 percent solution intravenously for two to four minutes. One method[33] calls for only one blood specimen two hours after the injection. This value is considered abnormal if the sugar content exceeds 140 mg per 100 ml, borderline if 120 to 140 mg and normal if less than 120 mg.

A more reliable method measures the disappearance rate of injected glucose. After an initial period of five to fifteen minutes, this rate of glucose decline is constant until about 60 minutes after injection.[34] Blood glucose is therefore determined every ten to fifteen minutes during this period and the fasting blood glucose concentration is subtracted from each value. The results are plotted on a semilogarithmic scale against time in minutes and the best fitting line is extrapolated to zero time. A line is then extended horizontally from half this value to the point of interception with the regression line, and the time at this intercept (t) is used to get the disappearance rate of glucose per minute (K). Hence, we have the formula[35]:

$$K = \frac{\log_e 2}{t(\min)} \times 100 = \frac{0.693}{t(\min)} \times 100$$

Some investigators do not subtract the fasting blood sugar concentration before plotting the decay curve. Normal and diabetic K values are listed in Table 4. Results in between are considered borderline. This method becomes more accurate if the K values are corrected for urinary glucose loss[36] or if a larger glucose load of 50 gm per 1.73 m^2 is used.[37]

Oral Cortisone-Glucose Tolerance Test—Many observers regard this test as still in the investigative stage. It is designed to determine the ability of the pancreas to enhance insulin secretion to overcome the inhibitory effect on glucose tolerance by an insulin antagonist. Since this test detects subclinical (latent) diabetes, it is superfluous if the standard oral glucose tolerance test is abnormal. In the past, this test has been used mainly to discover the genetic trait in people with a family history of diabetes, or in women delivered of infants weighing more than 9 pounds. Current thought, on the other hand, is that degenerative changes in the cardiovascular system are facilitated by defective insulin action before the standard glucose tolerance test becomes abnormal.[38] Therefore, it is a procedure that may be used in the future with greater frequency and may even find use as a screening test.[39] It is as yet unknown how many people with an abnormal cortisone-glucose tolerance will ultimately have diabetes. Although the originators of this test use cortisone,[40] other glucocorticoids have been used as well.[39,41,42] Only the method using cortisone pretreatment will be described here.

The patient is prepared in the same way as for the standard oral glucose tolerance test. Fifty milligrams of cortisone acetate is given by mouth eight and a half hours and again two hours before the 100 gm glucose drink (62.5 mg cortisone acetate each time if the body weight exceeds 160 pounds). Blood for glucose determination is drawn one, one and a half and two hours after start of glucose ingestion. Originally, a positive response was that in which the values exceeded 160, 150, and 140 mg per 100 ml, respectively, in these three specimens.[40] I believe that the higher values given in Table 5 represent more realistic criteria, with the area between negative and positive being called borderline. Of the three time intervals tested, the two-hour blood glucose value may prove to be the most important.[39] It must be mentioned that glycosuria is common with this test in normal persons, since glucocorticoids lower the renal threshold for glucose.

TABLE 4.—*Intravenous Glucose Tolerance Test*

	K Values (Disappearance rate of injected glucose in % per minute)	
	Subtracting FBS	*Not Subtracting FBS*
Normal	> 3.0	> 1.1
Diabetes	< 2.5	< 0.9

TABLE 5.—*Cortisone-Glucose Tolerance Test*

	Values in mg/100 ml		
	1 hour	*1½ hour*	*2 hour*
Negative Response	< 160	< 150	< 140
Positive Response	180 or more	160 or more	140 or more

TABLE 6.—*Tolbutamide Response Test*

	Values Expressed as % of FBS		
	20 minutes	*30 minutes*	*60 minutes*
Normal	< 75%	< 66%	72 ±12%
Diabetes	> 83%	> 74%	77 ±11%

Tolbutamide Response Test — This test was originally designed for the differential diagnosis of hypoglycemic states.[43] Since tolbutamide stimulates pancreatic insulin release, a diminished or delayed hypoglycemic response can be expected in diabetic persons. For the diagnosis of early diabetes this test is not as reliable as the standard oral glucose tolerance test. It may be used in the same circumstances as those for the previously described intravenous glucose tolerance test, namely, in patients who may have interference with oral glucose absorption. In the presence of known liver or kidney disease, this test is not only unreliable but may be dangerous and is, therefore, contraindicated.[44] The patient is prepared with a proper carbohydrate intake as described for the oral glucose tolerance test. After a fasting blood specimen is obtained, 1 gm of sodium tolbutamide dissolved in 10 to 20 ml of water is injected intravenously at a *constant* rate over two minutes.[43] Blood specimens are drawn at 20, 30, and 60 minutes after injection. The criteria for interpretation of this test are listed in Table 6. Normally there is a quick drop of the blood sugar concentration with return toward the fasting value in 60 minutes. In persons with diabetes, there is a slow fall, usually continuing steadily over 60 minutes after injection, but never reaching the low 20 and 30 minute levels attained in specimens from normal persons.

Blood Insulin Determination—This test, based on an immunoassay,[45,46] is now becoming commercially available. With the use of such assays, two broad groups of diabetic persons have been classified[47]: One where blood levels of insulin rise, particularly after a glucose administration, to higher than normal levels; and another where the rise is inadequate. The high insulin output group includes mostly obese persons with maturity-onset diabetes. These patients have primarily a defect in peripheral glucose disposal and are treated by strict dietary regulation and by phenformin, which affects peripheral glucose utilization directly, rather than by giving more insulin, which only tends to favor more fat deposition. Juvenile diabetic patients and lean persons with maturity-onset disease fall into the low insulin output group. Since patients in this category seem to have mainly a defect in insulin production, effective therapy should reasonably include exogenous insulin or agents stimulating endogenous insulin production. During an early stage of pre-diabetes, insulin values may exceed the normal range[48,49]; some time before actual decompensation occurs, ultimately leading to clinical diabetes, the immediate insulin reserve may be depleted, and lower than normal levels of insulin will be found.[50]

When blood specimens are drawn for insulin assay, the serum must be separated immediately and kept frozen until analyzed. The normal fasting range is between 5 and 30 μU insulin per milliliter of serum. Insulin is released by the pancreas in response to an increase in blood sugar concentration. The peak blood insulin level is normally attained one to five minutes after an intravenous glucose load. The level of insulin may, therefore, be most meaningful three minutes after glucose injection, administered as described under the intravenous glucose tolerance test above. The normal range during that period is 30 to 100 μU insulin per milliliter of serum.

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CARDIAC ARREST

"The diagnosis of cardiac arrest remains very simple: loss of consciousness and absence of pulse, respiration, and heart sounds. My only advice is: if you're not confident within a minute that a patient has *not* arrested, treat him as if he has. With the availability of closed chest massage, there's simply no need to delay institution of therapy. A patient may get a few broken ribs or a sore chest from being massaged if he doesn't need it, but it's not with the same implications as an open thoracotomy.

"The cardiogram is of no value in diagnosis because the heart will continue to have electrical impulses for some time after mechanical contractions have stopped. We've seen this repeatedly in the operating room. When the heart stops, the blood pressure cannot be obtained; but there are still feeble twitchings, and the cardiogram looks surprisingly normal. It therefore cannot be used to exclude the diagnosis."

—FRANK C. SPENCER, M.D., New York City
Extracted from *Audio-Digest Surgery*, Vol. 15, No. 19, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

Family Planning

KEITH P. RUSSELL, M.D., *Los Angeles*, AND GITTA MEIER, M.A., *Berkeley*

■ *Although the availability of oral contraceptives and the development of improved intrauterine contraceptive devices have greatly increased the general utilization of family planning services, there are still great segments of our population which are not yet reached, especially in the economically deprived areas. Since over 98 percent of all obstetrical deliveries now occur in hospitals, it seems logical that it is on hospital maternity services that these deficiencies might often be best overcome. Although this is primarily a medical problem, the use of paramedical personnel can greatly augment the physician's practice in these areas. Family planning services should be an integral part of comprehensive maternity care, not alone in the physician's office but also in the hospital setting.*

e Hospital Setting

The policy statement on family planning adopted by the California Hospital Association in 1968 gives formal recognition to the concern of hospital administrative and medical staffs for the provision of family planning services. The statement affirmed that "professional assistance with child spacing and family limitation information and service should be an integral part of a comprehensive maternal care program," and that "hospital boards and the medical staffs should seek opportunities to help develop needed family planning services." The California Hospital Association has thus become the first state-wide hospital association to join the American Medical Association, American College of Obstetricians and Gynecologists, American Public Health Association, American Nurses' Association, California Medical Association, California Conference of Local Health Officers, and many other organizations in strongly endorsing the inclusion of family planning assistance among the professional responsibilities of their members.

Although the advent of oral contraceptives and intrauterine devices has greatly increased the anticonception protection obtained from professional sources among all segments of the population, surveys have pointed up inadequacies in such protection among the poor and the poorly educated. On the basis of available information it has been estimated that in the United States between 4,600,000 and 5,300,000 women in the very low income group required reliable assistance with child spacing; only about 700,000 of such women were known to have been reached by existing family planning programs under hospital, public health, Planned Parenthood, and Office of Economic Opportunity (OEO) sponsorship during 1967.[2] Corresponding local estimates indicate that in California considerably less than one-third and possibly not more than one-fourth of women in the very low income group are receiving family planning assistance from professional sources.[5] Most of these women continue to resort to generally less reliable and less satisfactory non-prescription methods of fertility control. Unplanned, unwanted and problem-creating pregnancies still are a common occurrence for them, due both to failure of these methods, and to failure to use the methods correctly.

Family Planning Assistance Provided by Hospitals

Postpartum prescription of contraception has become a well established medical practice. It is of greatest value to women who did not have professional asistance with contraception earlier. The most strategic opportunity for orientation in family planning practices by these patients is offered at the time of prenatal and post-delivery contacts, followed by prescription before discharge from hospital or at the time of the postpartum check-up. For this reason, the obstetric and gynecologic services of hospitals in California must assume a major role in the delivery of family planning assistance, adding to and complementing the services already available through private physicians, health departments, Planned Parenthood, and OEO sponsored clinics.

Chairman, Committee on Maternal and Child Care, California Medical Association (Russell); Consultant, California Interagency Council on Family Planning (Meier).

Submitted 1 July 1968.

Reprint requests to: 266 South Harvard Boulevard, Los Angeles 90004 (Dr. Russell).

Services to Non-Private Maternity Patients

With some significant exceptions,* in California as elsewhere, systematic hospital-based family planning assistance has been limited (though not assured) to patients who are receiving their obstetric and other medical care as staff or ward cases rather than as private patients. For the most part, this includes those in two overlapping categories: county hospital patients and staff patients in teaching hospitals that have residencies in obstetrics and gynecology. The institutions in the latter group vary with respect to other important characteristics: for example, some are affiliated with or operated by medical schools, others are conducting independent residency programs; some are church-owned and controlled, some are county or city hospitals, others are non-profit or community hospitals. Most, but by no means all, report more than a thousand deliveries annually. For some, the bulk of deliveries involves staff patients; for others such deliveries make up only a minor fraction. Presumably, admission to obstetric care as a staff patient is based on income limitation in almost all of these hospitals; and from this it can be assumed that these patients fall into the medically indigent or very low income group.

What family planning services are these county hospitals and teaching hospitals providing at present? Preliminary estimates based on 1966 data of varying accuracy indicate that in the 29 California county hospitals which reported any sort of family planning services, over 44,000 deliveries occurred. Fewer than 20,000 of the patients involved were reported as having received even initial contraceptive assistance through the hospital. Over 10,000 additional births occured in the remaining county hospitals which did not report any family planning services for 1966. Among the hospitals reporting services, the proportion of maternity patients served ranges from about 60 percent of the total in one facility to 0.6 percent in another. In the majority of hospitals, less than one-third of new mothers appear to have received contraceptive assistance. Family planning services provided by health departments, farm workers' health centers, Planned Parenthood and OEO family planning clinics make up for some of these deficiencies, but reports from these agencies emphasize their inability to serve all these women effectively.

The American College of Obstetricians and Gynecologists, together with the Center for Population Planning of the University of Michigan, is surveying the family planning services provided by teaching hospitals throughout the United States. Preliminary analyses for California and other states point toward wide differences in the percentage of non-private maternity patients accepting contraceptive services among hospitals serving seemingly similar patient groups. Also, a significant proportion of these patients do not return for postpartum examination.[3] Some of those who do not return may be receiving six-week checkups or family planning assistance from their own physicians or from health department and planned parenthood clinics. However, in most communities even an optimistic estimate of family planning assistance received from alternate sources leaves an important segment of recent maternity patients in these hospitals unprotected against another pregnancy in the 12-month period following birth.[5] Yet, this is the period during which another pregnancy often is considered by physicians as undesirable in consideration of the mother's health.[7]

Experience throughout the United States has shown that the introduction of contraceptive services by hospitals where none was offered before will improve previously unsatisfactory return rates for postpartum checkups, and that a majority of women who do return will accept contraception at that time. Among the features directly related to family planning services that appear to contribute to satisfactory return and acceptance rates are:

- Emphasis by the OB/GYN department that contraceptive assistance is an essential and integral part of good OB/GYN and general medical practice.
- Utilization of prenatal clinics, and patient teaching sessions pre- and postnatally for discussion of family planning; discussion of the subject with each individual patient before discharge; written information for patients on available services and methods.
- Orientation of nursing and social work personnel, medical students and other house staff, and appropriate clerks and receptionists.
- Removal of restrictions with respect to marital status, age and residence of patients.
- Provision of family planning information and services to patients whose pregnancies did not terminate in live births.
- Scheduling of family planning services or clinics so as to facilitate attendance—for example,

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*Military hospitals now are including family planning assistance in their obstetric and gynecologic services for military dependents.

as part of the postpartum examination, or directly following postpartum clinic appointment; utilization of unavoidable waiting periods for patient teaching, movies, etc.; evening clinics; simplification of prescription filling procedures.

- Arrangements for return visits at the hospital or in clinics closer to patient's home for family planning assistance at free or part pay rates.
- Referral to public health nurses, visiting nurses or neighborhood workers for follow-up contacts; employment of a liaison nurse in the hospital for patient education and arranging referrals.
- Strong administrative backing and cooperation in the introduction and operation of family planning services, so as to make possible the organizational and budgetary adjustments required for an effective program.

The data collected by the California State Department of Public Health and the American College of Obstetricians and Gynecologists' survey of teaching hospitals provide only incidental information on other factors that are known to influence postpartum return rates and thus contraceptive acceptance rates: overcrowded, impersonal clinics, long waiting periods, cost and inconvenience of transportation to clinics, language barriers, frequent changes of staff, long-standing antagonism toward certain institutions on the part of that population depending upon them for service, and other similar factors. Those hospitals with very high postpartum return and acceptance rates among their maternity patients have been able to minimize or eliminate these impediments.

Services to Private Patients

Even before the introduction of the Medi-Cal program, a very substantial group of patients in the very low income group and patients who might be considered high pregnancy risks due to their age, parity or obstetrical history were not delivered in county hospitals or as staff patients in teaching hospitals, but as private patients in non-profit or proprietary hospitals. A preliminary analysis based on 1965 birth certificates indicates that about 45,000 women who were under 18 years of age, or had five or more children, or had late or no prenatal care (or a combination of these three) gave birth in such hospitals. A majority of these also are known to fall into the very low income group. With the implementation of Medi-Cal, much larger numbers of women in these high risk categories can be expected to register as private maternity patients.

Notwithstanding the growing professional concern with family planning, individual physicians still vary considerably in their emphasis on family planning, especially in the absence of patient request or obvious medical contraindications to pregnancy. Some are understandably reluctant to initiate contraceptive counseling with unmarried patients; others will not discuss family planning on account of religious convictions.[1] Moreover, not all private maternity patients return for postpartum checkup—when physicians traditionally may discuss family planning. It is also true that for a busy physician a really thorough discussion of family planning—preference as to number of children, choice of methods, problems of usage, and other aspects—can be very time-consuming, especially with a poorly educated patient. This combination of practical obstacles to a comprehensive orientation and provision of family planning services by physicians for their private patients points to the great potential contribution which the hospital staff, in close cooperation with the attending physicians, can make in this field.

Assistance for Other Patient Categories

The gynecologic services in most hospitals provide an important source of contraceptive assistance for women who have not recently given birth. In addition, many chiefs of obstetrics-gynecology are bringing new developments in fertility control and family planning services in their hospitals, to the attention of medical personnel in other departments. Operation of an active and visible family planning clinic in itself tends to generate greater interest in counseling and referrals.[4]

There is lack of information about the extent to which hospital discussion of contraception has become standard procedure with non-maternity patients in the childbearing age group, in the absence of serious medical contraindications to pregnancy or direct patient request. In some instances, no doubt counseling and prescription occur within the Internal Medicine department or some other specialty service. Discussion and referral appear also to be occurring with increasing frequency on the psychiatric services of general hospitals. Similarly, many pediatric departments in California and throughout the country have come to recognize their responsibility for the "primary prevention of pregnancy" among adolescents, as well as for "secondary prevention" among young mothers. On the other hand, patients and their spouses on leave or about to be discharged from institutions for the mentally ill or from tuberculosis sanitaria constitute important and definitive groups whose special needs for protection against unplanned pregnancies still are often neglected.

The Hospital as Source of Family Planning Information

With respect to family planning, as with many other health concerns, an important responsibility of hospitals is to provide up-to-date information and advice on various health services existing in the community. Thus, receptionists, switchboard operators and other staff personnel in direct contact with patients and the public should be able to offer appropriate and accurate information about sources of family planning assistance in the community. Requests for such information probably are most frequent in hospitals where family planning clinics with restrictions on eligibility for service are located. "Non-eligible" patients have been known to be turned away without referral to available alternative resources by hospital staff members who were unaware of the existence of such resources.

Most of the following suggestions include practices that already have been adopted in some hospitals, or by individual staff members:

- Inclusion, among the items of health information given to new mothers, of some of the many excellent brochures on family planning available through Planned Parenthood and various drug companies.

- Use of booklets on baby care which discuss resumption of intercourse and contraception. Many hospitals have prepared such literature for both private and non-private patients.

- Emphasis on the responsibility of the nurses on the maternity floor to ascertain whether the new mother wishes to discuss contraceptive methods and related questions with her physician before leaving the hospital, much in the same way as the nurses are expected to encourage patients to discuss questions related to diet or various aspects of baby care. In turn, the nurses would have the additional responsibility of calling to the physician's attention any fears, doubts or questions in this area the patient might have.

- Use of up-to-date films or tapes on family planning in parents' classes and in formal or informal sessions on the wards.

- With consent of the patient's physician, referral to public health nurses or visiting nurses of patients for whom medical or other contraindications to rapid order pregnancies exist. Before Medi-Cal, many such patients would have been assured of routine home calls by public health nurses who would have discussed family planning with them. Now this additional reminder and orientation will not be available to them unless their physicians or someone assigned that duty in the hospital make special arrangements for such follow-up contacts.

All of the foregoing suggestions require a measure of staff education and orientation so as to clarify the respective responsibilities of all concerned within the hospital. In most hospital settings, nurses will be the staff members most frequently involved in this patient orientation. It is of interest here that the California State Health Department's nursing consultants, on the basis of their contacts with nurses staffing private units, report a growing concern on the part of the latter nurses for more systematic involvement in these activities. At the moment, many nurses are held back by the lack of clear instructions from hospital administrations and medical staffs.

In some hospitals, other heavy demands on nursing time may favor the utilization of public health liaison nurses or appropriately supervised and trained volunteers or sub-professional staff, to discuss family planning with maternity patients.[6] In hospitals with social service departments, social workers have already assumed responsibilities for systematic counseling and referrals, or can be encouraged to do so. In this connection, suggestions for family planning education and services in hospitals and source material for staff orientation are currently being prepared by the State Health Department's Bureau of Maternal and Child Health.

Conclusion

Logistic reasons alone argue for a strong emphasis on family planning in the hospital setting, most particularly in hospitals with obstetric services. Logistic reasons of a different sort have led to the expansion of neighborhood-centered family planning services, together with increased emphasis on contraceptive assistance provided by physicians in private practice. It is important that these be complementary developments, rather than alternatives.

As with many other hospital services, the lack of funds, space or qualified staff so far has prevented or hampered the development of optimal family planning assistance in most hospitals. The recent allocation of federal funds for family planning projects under both public and private auspices provides a new incentive for hospitals to introduce these services and to expand and improve existing services. It is anticipated that many California hospitals will join health departments and other community agencies in developing programs which will qualify them for Children's Bureau or Office of Economic Opportunity grants for this purpose, as is already happening in Los Angeles County through the Los Angeles Regional Family Planning Council, Inc.

The responsibility of hospitals and of hospital staffs needs to go beyond the development of these specialized programs. It is confidently expected that the recognition provided by the California Hospital Association's recent policy statement will serve, as stressed in its introductory paragraph, "to facilitate the efforts made by physicians, nurses and others directly involved with providing family planning assistance and increase the availability of information and services to the many individuals not so far being reached."

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TROUBLE-MAKING ELECTRONS

"If the electrical equipment we use today in the operating room is not properly grounded, it is very easy with infinitesimal currents to produce ventricular fibrillation. It is particularly easy if the equipment is not properly grounded to produce burns, and these burns will go through your EKG leads if that serves as the ground for the cautery. If the cautery's ground is defective and you're monitoring with an EKG, then the contact point of the EKG becomes the ground for the cautery, and you get a burn because the current density is strong enough. It's that simple. But that's just a burn. The others will produce ventricular fibrillation. . . . This is something you have to be aware of."

—Valentino D. B. Mazzia, M.D., New York City
Extracted from *Audio-Digest Otorhinolaryngology,* Vol. 1, No. 5, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

Heart Sound Screening in High, Low and Middle Income Communities

MARVIN L. AUERBACK, M.D., *San Mateo*

■ *Heart sound screening was performed on elementary school children in three San Mateo County communities, using the Phonocardioscan, a portable analog-digital computer. Although these communities differed significantly in socio-economic backgrounds, the incidence of previously known and unknown heart disease was not dissimilar. However, there was an unusual difference in community reaction to the heart sound study, with the families in the middle class area exhibiting more anxiety than those in the high and low income communities.*

THE PHONOCARDIOSCAN* has been used in a number of communities to detect heart disease in children and has produced valuable quantitative and qualitative information on the presence of heart defects.[1-3] In most of these studies, however, there has been no correlation of findings with the socio-economic background of the children or community reaction to such screening programs.

This is a report of my experience with the Phonocardioscan with pupils in the third and fourth grades in three elementary school districts in San Mateo County. The study embraced represents high, middle and low income groups in one of the wealthiest counties in the United States.

Procedure

The Phonocardioscan is a 20-pound transistorized analog-digital computer with heart sound circuitry engineered to detect systolic murmurs greater than Grade 1½ systolic (scale of 6); high and low frequency diastolic murmurs; and second heart sounds more widely split than 50 milliseconds. There is a single concomitant electrocardiographic timing lead obtained by placing two suction cup electrodes on the chest in the seventh interspace, mid-clavicular line, bilaterally.

By using a small velocity microphone placed consecutively at the apex and the fourth, third and second interspaces, left sternal edge, abnormal findings are conveyed to the technician by a series of flashing lights. These can be counted automatically by a special counter built into the system or, as in this study, counted by the technician and then recorded. There is no print-out by the computer. All sounds are recorded in mid-expiration.

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This study was supported in part by a grant from the San Mateo County Heart Association. The Phonocardioscan was loaned by the California Heart Association.

Submitted Revised 9 Sept. 1968.

Reprint requests to: 19 West 39th Avenue, San Mateo 94403.

*Humetrics Division, Thiokol Corporation, Los Angeles.

Any child who caused the lights to flash consistently on the computer in any part of the cardiac cycle was re-screened by another technician on another day. Children who continued to show phonocardioscan abnormalities were then evaluated by me at their schools on still another day. Then, the children were examined in both sitting and recumbent positions, and the presence of any murmurs and of any unusually wide-splitting of the heart sounds or rhythm disturbances was noted. Femoral and radial pulses were also palpated. Maneuvers, such as the Valsalva, were used repeatedly to help differentiate between functional murmurs and those that seemed significant. Presumably from these observations a board-certified pediatric cardiologist could make a fairly educated clinical assessment. Nevertheless, since electrocardiograms and x-ray films were not made routinely on these patients, but only on those considered to have organic disease, it is possible that some organic murmurs were designated as functional. Undoubtedly, any errors should come to light eventually.

Brief questionnaires were sent to all parents of third and fourth graders who were examined in the three elementary school districts of the county. These solicited brief information—history of heart disease, rheumatic fever or heart murmurs—and requested permission to screen the child with the Phonocardioscan.

The Communities *(Table 1):*

San Mateo County is immediately to the south of San Francisco and is a middle class residential county with strong agricultural ties. It has areas of extreme elegance and affluence, and others of relative poverty. Even in the low income sections of the county, most people have a one-family dwelling, an automobile, and the opportunity to send children to a well-equipped school. Relatively, however, there is a considerable gap between the rich and the poor districts of this county. The three communities studied were Hillsborough, Belmont and East Palo Alto.

Hillsborough lies 15 miles south of San Francisco, has no commercial endeavors, and remains a residential community with an average income among the top five in the United States. Its main product is children, who are extremely well cared for; there is an excellent elementary school system. The parents tend to be conservative but anxious for the best for their children. Even though every child in the school population had his own personal physician (usually a pediatrician) and had been seen repeatedly through the years, the families were pleased to have the children evaluated by the computer (only two percent refused). There was little anxiety that the computer would discover any previously undetected heart disease.

Belmont, 24 miles south of San Francisco, and only five miles from Hillsborough, is a middle class community whose population has quadrupled since 1950. It has some commercial enterprises but, for the most part, it houses the commuters who use the Southern Pacific trains or the Bayshore Freeway into San Francisco each day.

The parents, like their counterparts in Hillsborough, want only the best for their children. They take an active part in Parent Teachers Association and other school activities, but in general they are more anxious about their children than the Hillsborough parents, and are particularly upset if they find that they differ in any way from the average. They exhibited more anxiety about the testing program, and a higher proportion (four percent) refused to have the computer used on their children. Some of those who refused did so with much vehemence, and even threatened to keep the children home from school the day the Phonocardioscan was used, to be sure they would not be studied. Local physicians received phone calls from parents asking whether or not they should permit the study to be done. This was not the case in Hillsborough, even though parents in both communities received almost identical information about the proposed study. I cannot explain this difference in reaction.

East Palo Alto-Ravenswood: This district draws its pupils primarily from East Palo Alto, a large neighborhood of 80 percent non-Caucasians, and of significantly lower income than the other two communities (Table 1). There are no pediatricians there, relatively few physicians of any kind, and many people visit local clinics instead of private physicians for their medical care. Because the children in this community do not have the continuity of care of children in Hillsborough and Belmont, I felt that a survey of the third and fourth grade students with the Phonocardioscan might be beneficial but made the mistake of approaching the district in the same manner as the other two communities, that is, "I wished to do a study." This was a serious error, as a "study" was not wanted. For some time, "doing a study" in East Palo Alto had become almost a way of life for researchers who periodically garnered Federal and other grants,

TABLE 1.—*San Mateo County Population Statistics**

	Hillsborough	Belmont	East Palo Alto
Total population	8,650	25,100	25,650
Annual family income (average)	$31,500	$10,000	$6,350
Family home value (average)	$75,000	$32,500	$9,500
Percent of school population			
Caucasian	99.1	98	20
Non-Caucasian	.09	2	80

*From San Mateo County Department of Vital Statistics.

came into the community, did their project, retired to create their theses, and never returned with the solutions to the problems they had encountered. The residents of East Palo Alto had put up with these studies with remarkably good grace but when nothing of significance was done to alleviate the problems this good-natured acceptance faded. By the time I presented my project, there was open hostility.

Helped by sympathetic persons who gave me some insight into the views of the community, I made an entirely different presentation that emphasized the positive aspects of the project—that is, to discover whose hearts needed attention so that care could be given. With this shift from "study" to "care," opposition abated — only three percent of the parents refused to cooperate.

Results *(Table 2):*

Hillsborough: One child was found to have congenital heart disease by the Phonocardioscan, but was already known to have the condition (a small atrial septal defect). No previously undiagnosed cardiac lesions were discovered. Functional murmurs were found in only three percent of the children, although the true incidence of functional murmurs was probably higher. More than three percent of the children were picked up on the original screening with the Phonocardioscan; with re-screening, the number dropped to the three percent level. This is not unusual when one considers the variability of functional murmurs, particularly their relation to physical or emotional stress. Many children who were obviously disturbed the first time they encountered the Phonocardioscan were noticeably less upset on re-screening. Admittedly, even with this explanation, the incidence of functional murmurs was quite low.

A group of eleven children (four percent of the total) who were reported by their parents to have either a heart murmur or heart disease, were consistently passed as normal by the Phonocardioscan. When these children were evaluated at school, I found only a Grade 1 systolic murmur without any evidence of organic disease. However, no electrocardiograms or x-ray films were made for evaluation beyond this clinical opinion. These children with the positive history but negative Phonocardioscan findings were, therefore, considered to have been "de-labelled" from the stigmata of heart disease. Several volunteer mothers (for the study) were visibly relieved to see the computer pass their children as normal when they had been thought to have a murmur of significance. Obviously, this process of "de-labelling" could be exaggerated and should be accepted with some reservations.

The study was well received, and follow-up questioning of parents, school administrators and physicians revealed no tension or anxiety had been created in parents or children.

Belmont: In decided contrast to those of Hillsborough and East Palo Alto, the children in Belmont showed a significant level of anxiety during the study. A number of children were reduced to

TABLE 2.—*Data on Phonocardioscan Screening in Third and Fourth Grades in San Mateo County*

	Hillsborough		Belmont		East Palo Alto	
	No.	%	No.	%	No.	%
Total number of students	275		676		1045	
Number refused Phonocardioscan	6	2	24	4	34	3
Phonocardioscan positive	10	3	59	9	89	9
Organic disease	1	0.4	6	0.9	11	1
Previously known	1	0.2	2	0.3	2	0.1
Previously unknown	0		4	0.6	9	0.9
Functional murmurs	9	3	29	4	72	7
No murmur detected, although Phonocardioscan positive twice	0		24	4	6	0.5
Phonocardioscan negative but history of heart disease or murmur (the "de-labelled" group)	11	4	15	2	16	1

tears; one child fainted. That this anxiety was not limited to the children was indicated by frantic calls from parents as to why their children required more than one screening. With few exceptions, the children all had personal physicians (generalists or pediatricians) who had examined them a number of times, yet they were surprisingly uneasy in the test situation.

The incidence of organic heart disease in these children is skewed somewhat by the fact that two of them had already had corrective operations on the heart. The other children with organic disease had previously undiagnosed defects (a small ventricular septal defect, likely of the muscular portion of the septum, and congenital aortic stenosis, probably of moderate severity).

Five percent of these children had functional murmurs, many of which seemed related more commonly to the outflow tract of the left ventricle (that is, near the aortic valve) than the outflow tract of the right ventricle. These murmurs were often of diamond-shaped, crescendo-decrescendo character, Grade I-II intensity maximal in the left fourth interspace, left sternal edge, but also well heard in the suprasternal notch. There was no thrill, no ejection click, no diastolic murmur nor any change with the Valsalva maneuver. Other functional murmurs were the usual vibratory type heard well at the second and third interspaces, left sternal edge, and unassociated with significant splitting of the second heart sound or with any diastolic murmur. These were readily changed by the Valsalva maneuver.

Fifteen children who were thought to have heart murmurs of significance were passed as normal ("de-labelled") by the Phonocardioscan.

East Palo Alto: My original thesis that there was probably more previously undetected heart disease in East Palo Alto than in Hillsborough proved correct, but by a rather slim margin. Nine children had such lesions as bicuspid aortic valve, aortic or pulmonic stenosis and small ventricular septal defects, none of which appeared to be of major hemodynamic significance. They will be evaluated further. It is unlikely that they will ever need surgical repair, but it is possible that chemoprophylaxis at the time of any operations in the mouth might be indicated to prevent subacute bacterial endocarditis. Seven percent of the children had functional murmurs discovered by the computer. As no examination of the blood was done, it is not possible to say whether some of these might have been due to nutritional or sickle cell anemia.

In general, these children accepted the study with little apprehension, and the schools reported no parental anxiety.

A smaller proportion of children (1.6 percent) were de-labelled in East Palo Alto than in the other two communities.

One child, in whom abnormality was picked up by the computer, proved to have an unusual case of acute pericarditis. She was well and attending school without complaint when she was found by the Phonocardioscan to have abnormal sounds in both systole and diastole. My examination the following day confirmed the presence of a friction rub, and she was admitted to the hospital. (A brief resumé of her unusual hospital course is described in the Addendum.) It is obvious that the discovery of this acute cardiac illness by the computer was purely fortuitous and cannot be used by itself as justification for cardiac screening. It does illustrate, however, a random finding of a kind that can be expected in any large volume screening project.

Discussion

Should heart sound screening be used routinely in elementary schools? It is certainly less expensive to use a computer to scan the children than to have pediatricians or cardiologists listen to hundreds of hearts or to tape-recordings of heart sounds. The San Mateo study averaged 85 cents per child. There is also the element of fatigue. Physical auscultation of many children cannot be done by one person for extended periods; whereas, the computer does not tire and remains reliable. Studies have shown that while the Phonocardioscan is not as accurate as a cardiologist, it can select cardiac lesions better than a general practitioner or general pediatrician.

Children with unknown cardiac lesions should be detected before they start the exceedingly vigorous physical training in school that is usually initiated at the fifth or sixth grade levels. In the affluent middle class districts, where children generally receive regular medical care, the likelihood of finding previously unknown cardiac defects is not great. For the occasional defect that is discovered, there remains the question of how much anxiety and tumult has been created by the mechanics of the study. Middle class parents, in particular, tend to be very apprehensive about their children if they vary from the norm. The attitude toward the

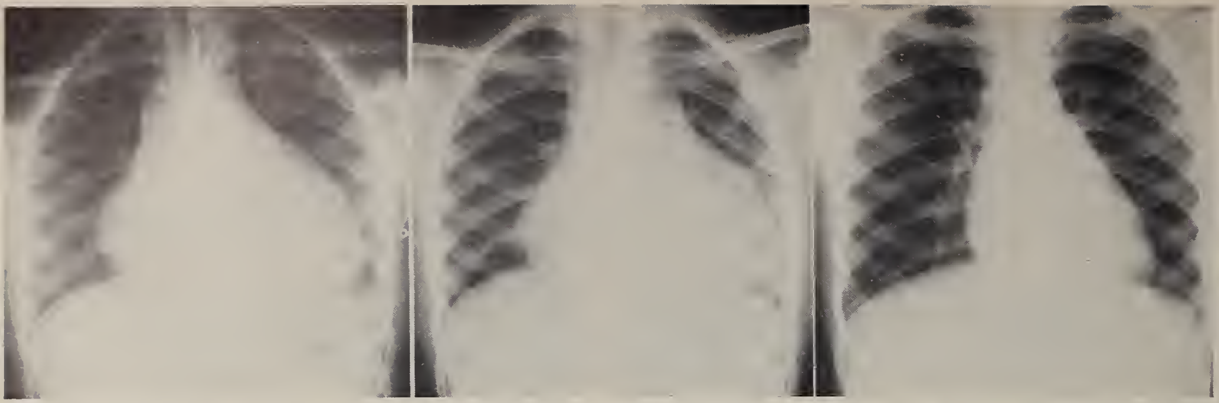

Figure 1.—X-ray films of chest taken on the first (left), third (center) and ninth (right) hospital days, showing evolution of the pericardial effusion.

computer evaluation of the heart was no exception; the ratio of worried parents in Belmont to the small number of previously unknown lesions detected is a distressing observation.

The generally good acceptance of this procedure by the less affluent community suggests that if a study is presented in the right way and the help which will result is emphasized, screening of children with the Phonocardioscan in such communities can be acceptable and prove of value.

It must be further emphasized that any study must be carried out by well trained technicians under close supervision of a cardiologist or cardiac-oriented pediatrician.

The advent of the Phonocardioscan represents an interesting beginning of the computer age in medicine. Any problems involved in its direct application to the living subject will certainly be overcome, and spectacular achievements can be expected to result in all medical fields. Particularly, the Phonocardioscan can be an important tool in detecting heart disease among children throughout the schools as well as in the various programs for poor people throughout the country.

Addendum:

The Phonocardioscan showed both systolic and diastolic murmurs in an asymptomatic 9-year-old girl. My examination revealed a friction rub and she was, therefore, admitted to the teaching service at San Mateo General Hospital. An x-ray film of the chest showed a large cardiac shadow consistent with pericardial effusion (Figure 1). Since the patient was still asymptomatic, no therapy was instituted; instead, she was carefully watched by the resident staff. She did well for 48 hours then became critically ill, with tamponade. X-ray films showed increased cardiomegaly. She was immediately given large doses of steroid intravenously, and within a short time improved clinically and radiographically. One can only speculate that the course of disease might have been less benign had she first arrived at the hospital when she was critically ill.

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Medicine and Environmental Health

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■ *Environmental threats to health and welfare are receiving much attention today and will become an even greater concern in the future. Since they often are the only group able to produce much of the basic data concerning environmental health effects, physicians must become more involved in environmental health problems, individually and organizationally. The Linton Report offers one proposal for attaining a liveable environment and should be reviewed by all health professionals.*

IT IS TIME for the medical profession to become even more involved with the problems of our environment, especially as they affect health, physical and mental. The physician is being called upon, with greater frequency and urgency, to bring his expertise to bear on the complex problems which arise from our increasing demands for goods and services, our technological and urbanized society, and our growing population. Often he is the only one who can begin to deal with some of the unanswered questions. Answers must eventually be developed if we are to intelligently deal with what has been described by some to be a threat to the existence of mankind.

On the other hand, we cannot and must not wait until all the answers are in before attempts are made to correct the misuse of our environment. Programs must be established which will, at a minimum, ensure that environmental quality will not deteriorate further.

AMA Council on Environmental and Public Health

The American Medical Association established a Department of Environmental Health and a Council on Environmental and Public Health in 1963 to be responsible for "Medicine's interest in the relationship of man to his surroundings," including communicable diseases, air, water, noise and soil pollution, radiation, solid wastes, urbanization and technological developments.

The Council's main contribution to environmental health is in the form of national congresses and conferences. A series of annual congresses examines environmental health problems of current interest. Some of the problems which have been studied at these congresses have been the feasibility of solving environmental health problems through engineering projects, changing patterns in environmental health, relationships between environmental factors and accidents, and management approaches to environmental health problems.

Air pollution medical research conferences are convened biennially for the purpose of bringing together experts to discuss the current data and theories regarding the effects of air pollution on health. The series of conferences was begun in California by the State Health Department. In 1966 the American Medical Association was invited to assume sponsorship of the series.

The Council on Environmental and Public Health also sponsors a series of annual symposia. Each symposium is directed to a particular public

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Presented as part of a Round Table on Planning for a Healthful Environment at the Environmental Health Conference, presented at the 97th Annual Session of the California Medical Association, San Francisco, March 23 to 27, 1968.

Reprint requests to: Department of Environmental Health, American Medical Association, 535 N. Dearborn Street, Chicago, Illinois 60610.

health problem. Past symposia have dealt with such problems as venereal disease control, immunization and obesity.

The Council has a joint subcommittee with the American Institute of Architects for the purpose of interacting with the architectural profession in an attempt to ameliorate some of the environmental health problems.

The result of these congresses, conferences and symposia are position statements of the Council, technical research papers, and information exchange with experts in the field, and subsequently a better informed profession and public.

In a recent survey of state medical societies to ascertain their degree of activity in the areas on environmental and public health, the following distribution of standing committees were found:

	States
Environmental Health	5
Air Pollution	2
Water Pollution or Sanitation	1
Pesticides and Poison Control	2
Radiation Safety	7
Automobile or Driver Safety	22
Advisory to State Licensing Dept.	8
Public Safety and Accident Prevention	11
Blood Banking	23
Public Health	30
Communicable and Infectious Diseases	6
Venereal Disease	9
Immunization or Preventive Medicine	9
Tuberculosis or Pulmonary Disease	24
Occupational Health	20
Industrial Health	14
Advisory to State Board of Health	13
Rural Health	35
Maternal and Child Welfare	15
School Health	15

This record, in my opinion, is not very impressive. Each and every state medical society should establish one or more standing committees dealing specifically with environmental health problems.

Four factors are necessary when a state society develops a committee concerned with some facet of environmental health: (1) an initial awareness of the problems at the local level; (2) establishment of a position toward the problems; (3) action at a professional level; and (4) participation in community action.

The "Linton Report"

There is a document which attempts to define some of the more serious environmental threats to health and welfare. It is by no means complete nor does it offer final answers. It is, however, an attempt to emphasize those problems which need immediate attention and outlines a strategy to attain partial solutions to them. That document is the report of the Task Force on Environmental Health and Related Problems, which was made to the then Secretary of the Department of Health, Education, and Welfare, John W. Gardner. The report bears the title, "A Strategy for a Livable Environment." It is, however, most often associated with the name of the Task Force chairman, Mr. Ron M. Linton, and called the "Linton Report."

Dr. Gardner has resigned from his post as Secretary of HEW to devote his energies to solving the urban problem in a manner he feels will be more fruitful, namely, through the Urban Coalition. Apparently Mr. Linton also feels this route will be expeditious, for he recently obtained a leave of absence from his post as Director of Special Projects of the Urban America Corporation to join Dr. Gardner at the Urban Coalition.

I believe that even in the absence of the principals, the report, "A Strategy for a Livable Environment," stands as a worthwhile attempt to outline a course of action for recreating a healthful, livable and enjoyable environment.

On 1 November 1966, Secretary Gardner commissioned the formation of the Task Force on Environmental Health and Related Problems to determine approaches to protecting man from the threats of environmental damage to his health and welfare. Rather than spend a great deal of time attempting to define or document environmental hazards, the Task Force elected to gather together the needed information by seeking the counsel of authorities on the subjects of concern. To this end, five two-day meetings were held (between December 1966 and March 1967) in Boston, New York, Detroit, Los Angeles and San Francisco.

Experts from educational institutions, state and local governments, private industry, and foundations and research institutions were invited to advice the Task Force on environmental problems and what ought to be done about them.

The Task Force convened nearly a dozen informal conferences in addition to the five formal conferences. Interviews and correspondence were conducted with other experts, including those in other Federal agencies.

From the basic data thus gathered, the Task Force attempted to develop recommendations to the Secretary. In developing these recommendations, the Task Force needed to make two basic decisions. One was that man should be capable of halting his contribution to environmental pollution. The other was that the time for action is now. Action must be taken with what knowledge and technologic ability we have, rather than await all answers to all questions.

On the basis of these two decisions, the report of the committee was channeled in two directions —one to identify environmental hazards needing immediate action and determine what initial steps offer the most immediate returns; and the other to create a system by which new goals can be developed and met in the future.

The report contains 34 principal recommendations, ten of them action goals, ten dealing with the creation of an environmental protection system, and the remaining 14 miscellaneous recommendations which support the goals and system.

Action Goals

The recommended ten action goals are steps which, in the opinion of the Task Force, must be taken immediately by the Department of Health, Education, and Welfare if it is to meet its responsibilities for the future. The proposed ten action goals were not intended to represent the only matters of concern, but were felt to represent a manageable series of steps which could yield beneficial results as rapidly as possible and to deserve the highest priority.

Air Restoration Goal

From the scientific evidence linking air pollution to major respiratory diseases and with the demonstration of extensive economic losses resultant from air pollution, the Task Force recommended that:

> ". . . . the Department undertake an effort to initiate by 1970 in 75 interstate areas abatement plans to reduce plant stack emissions by 90%, and to establish national standards to reduce vehicle exhaust emissions by 90% from 1967 levels through enforcement and a technological development program to provide the equipment necessary to meet the standards."

The Task Force noted further that the Clean Air Act and amendments are sufficient to permit an acceleration and expansion of HEW's air pollution activities. They therefore further recommended that:

> ". . . . the Department seek authority to provide air pollution program grants only to those control agencies which develop emergency plans that would control combustion activities under certain air pollution alert conditions."

Water Quality Goal

Quoting figures of 50 million and 45 million persons who drink water that does not meet Public Health Service standards and that has not been tested by the Public Health Service, respectively, the Task Force recommended that:

> ". . . . the Department undertake an effort by 1970 to test all existing and proposed public drinking water supply systems and produce meaningful public drinking water standards which, through an enforcement program, will ensure health-approved drinking water for 100% of the nation's public systems."

Waste Disposal Goal

Reviewing the mounting problem of solid wastes, the Task Force reported figures of production of 150 million tons of solid waste in 1965 and projected a level 250 million tons annually by 1980. To head off the predicted inundation, the Task Force recommended:

> ". . . . an effort to provide by 1973 a grant-in-aid program for solid waste disposal at the local level; a developmental research program to integrate solid and liquid waste disposal and air quality control; and for the disposal of nuclear wastes."

Population Research Goal

Environmental pollution was concluded to be attributed mainly to man and his misuse of his environment. The Task Force points out that in spite of the current planning for environmental management, a serious oversight exists. That oversight was stated to be the lack of study of the effect of population growth and pressure on the planning and conduct of environmental protection programs. The Task Force therefore recommended:

> ". . . . an effort to determine by 1968 the effects of population trends on environmental protection goals and programs as part of the basis for setting Department objectives with respect to family planning and population dynamics."

The Task Force further recommended:

> ". . . . the acceleration within the Department of Health, Education, and Welfare of a national family planning program to disseminate family planning information to all requesting state and local health agencies, physicians, private associations, and individuals."

Urban Improvement Goal

The Task Force felt that the present urban environment is a threat to man's physical, mental and social well-being by virtue of the stresses placed on him by noise, crowding, odor, traffic and other insults. It was, therefore, recommended that:

> ". . . . by 1973, the Department develop, through research, basic data sufficient to establish human levels of tolerance for crowding, congestion, noise, odor and specific human endurance data for general stress and accident threats, including traffic, home, and recreational accidents."

Further,

> "The Task Force recommended that the Department develop urban and rural model codes and suggested standards for the prevention and control of various sources of noise in the environment."

Materials, Metals, and Chemicals Control Goal

Materials, metals, and chemicals with known or suspected harmful effects were said to be marketed at an ever increasing rate. Little was said to be known regarding their adverse effects on allergic disease, chronic diseases, or long-term genetic changes.

The Task Force therefore recommended that:

> ". . . . an effort to establish by 1970 human safety levels for synthetic materials, trace metals, and chemicals currently in use and prohibit after 1970 general use of any new synthetic material, trace metal, or chemical until approved by the Department of Health, Education, and Welfare."

Consumer Protection Goal

The Task Force recognized that there are many new products available on the consumer market, which even in normal usage could be hazardous to human beings. The Task Force therefore recommended:

> ". . . . an effort which, by 1970, will initiate a comprehensive program for the identification of health and safety hazards associated with the use of appliances, clothing, food, hazardous substances, and other consumer products and for the control of such products which fail to meet consumer protection standards established by the Department."

Radiation Control Goal

In order to minimize the potential damage from devices, which generate x-rays, either as their primary function or as a secondary by-product, and from nuclear materials, the Task Force recommended:

> ". . . . an effort which, by 1970, through developmental research and enforcement, adequately protects workers and the public from harmful radiation levels."

Occupational Health and Safety Protection Goal

In order to more fully protect the American worker, the Task Force recommended:

> ". . . . an effort to extend, by 1970, preventative services to 100% of the employed population at its work place."

Government Compliance Goal

The necessity of intergovernment cooperation to promote and carry out environmental health programs led the Task Force to recommend:

> ". . . . an effort which, by 1969, through effective relations with local, State, and federal governments, will ensure that criteria and standards for physical and mental health, for housing, urban development, and transportation will be available and used by federal agencies administering these programs."

In looking beyond remedies for the immediate concerns as outlined in the ten action goals, the Task Force described a plan to permit the setting of new goals as environmental conditions change. Recommendations were made regarding mechanisms by which such new goals could be established and how their objectives could be determined and supported.

Briefly the recommendations were to:

- realign DHEW along functional lines rather than the current catagorical approach. The functional elements were outlined as:
    - —research and development
    - —determination of standards and criteria
    - —enforcement
    - —manpower development
    - —public awareness
    - —intergovernmental relations
- contract with universities or research institutions or both to encourage large-scale, long-term health related studies in human ecology
- create, through contracts, a nonprofit research organization responsible to DHEW
- establishment of an Office of Assistant Secretary of Research and Development
- establish a support mechanism for development and operation of urban sociological health research centers

- develop and implement an Environmental Protection System functionally oriented to establish:
  - —environmental surveillance and associated basic research
  - —criteria and promulgation of standards
  - —developmental research
  - —compliance

The Task Force encouraged the establishment of the Environmental Protection System by recommending that the Secretary of HEW call upon the President to seek congressional approval of an Environmental Protection Act. This Act would establish a Council of Ecological Advisors which would keep the President informed of various agency programs and help coordinate such programs. The Council would be similar to the Council of Economic Advisors which now serves the President.

These are some of the recommendations made by Mr. Linton's committee. We may or may not agree with all of his suggestions or with the order of priorities, but at least we now have a starting point.

DEALING WITH RUPTURED ABDOMINAL AORTIC ANEURYSM

"When a patient with a ruptured abdominal aortic aneurysm arrives at the hospital, he should not be put on a table or an examining cart in the emergency room. He should be taken immediately to the operating suite. O-negative blood should be used if the patient is in shock, rather than depending on a cross-match which may take time. The anesthesiology group and the residents should be capable of getting in a litre of blood a minute through several routes, at least one of which should be above the inferior vena cava, that is, in one of the arms. One can control the hemorrhage rather well simply by pressing the thumb hard against the aorta above the colon until he can put a clamp across it. The basic thing then is rapid transport to the operating room, prompt operation with O-negative blood, and control of the bleeding."

—James D. Hardy, M.Sc., M.D., Jackson, Miss.
Extracted from *Audio-Digest Surgery*, Vol. 15, No. 19, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

Prevention of Rh Hemoly

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■ *Rho(D)-Immune Globulin was given to 322 Rh-negative women delivered of ABO-compatible, Rh-positive infants with no apparent failures to suppress Rh sensitization. In contrast, 32 of 305 mothers of a control group made Rh antibody during the six months following delivery. In subsequent pregnancies, 69 women administered RhoGAM had no evidence of isoimmunization after delivery while six of forty mothers of the control study produced anti-Rh. RhoGAM, given within 72 hours of delivery in the amounts employed, was effective for suppression of Rh immunization.*

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Supported by Grant No. HD-01504-01 from the National Institutes of Health, Public Health Service, U.S. Department of Health, Education, and Welfare.

Submitted, revised, 17 Oct. 1968.

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Author's Note: This is the original version of the paper "Prevention of Rh Hemolytic Disease of the Newborn," a portion of which was published in Transfusion, 8:146-148, May-June, 1968, under the title, "Long Beach (California) Experience with Rh Immunoglobulin."

sease of the Newborn

THERE IS NOW abundant evidence that Rh sensitization can be suppressed with human anti-Rh gamma globulin given intramuscularly in sufficient amounts.[2-4] Our interest in this subject began in the autumn of 1964 when we sought answers to the important questions related to fetal-maternal hemorrhage and its significance in Rh antibody formation. We have reported our observations,[5] which confirm those of others,[6-8] that most fetal hemorrhages occur during labor and at the time of the separation of the placenta from the uterine wall. The differences between hemorrhages in the antepartum period and immediately postpartum are even more apparent when one considers only large hemorrhages. The incidence of these observations is increased at least nine-fold when compared with the findings during gestation.[5] It was important to establish the time of these microhemorrhages as background information to justify clinical trial of gamma globulin to be given during the immediate postpartum period.

The second question related to the significance of fetal-maternal hemorrhage as detected by the Kleihauer technique (modified by us),[5] in relation to antibody production. Our studies have indicated that these observations are valid and bear a strong relationship to the likelihood of antibody production, and further, they can be utilized to delineate a high risk group of Rh-negative mothers.[9] These studies, then, with those of others, have confirmed that most fetal-maternal hemorrhages occur during labor and that these are directly concerned with the development of Rh sensitization.

Another observation reported by us is of interest because it is in conflict with time-honored concepts as to when sensitization occurs.[10] For many years it was believed that, in the absence of transfusion, the first appearance of Rh antibody ordinarily occurred during the second pregnancy. We now know this not to be true, for our studies have shown that anti-Rh appears commonly *after* the first pregnancy (incidence 11.5 percent in the control group) and that none of 24 patients followed by us in subsequent pregnancies in our control group developed antibody *during* the second pregnancy. In our study of 410 Rh-negative primiparas who had not had transfusion, only one developed antibody during the first pregnancy which was apparent in the immediate postpartum period. Ordinarily antibody first appeared three months postpartum and was usually still demonstrable six months after delivery. There was no uniform pattern with regard to the serologic reactions of antibody when it first appeared or during the periods of observation that followed. It is to be emphasized that all patients in whom antibody was noted during the subsequent pregnancy had detectable antibody following the previous pregnancy.

Material and Methods

The purpose of this report is two-fold: to record the research plan that has been utilized in Long Beach, California, and to report the results of our efforts to suppress Rh isoimmunization with Rh_0-(D)-Immune Globulin (Human) — RhoGAM.* The material used in this study was provided by the Ortho Research Foundation and was identical to that utilized in the studies reported by Freda and coworkers.[3] The women were private patients delivered of infants in the major hospitals in Long Beach. Each morning the hospitals supplied information about Rh-negative women who during the previous 24 hours had been delivered of Rh-positive infants with no evidence of Rh hemolytic disease.

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*Trademark—Ortho Diagnostics.

All laboratory work reported in this study was done by technologists of the research team of the Department of Pathology of Memorial Hospital. Only Rh-negative mothers who had been delivered of ABO-compatible Rh-positive infants and who had not made anti-Rh were admitted to the study. An additional criterion was that the direct antiglobulin test done with cord blood be negative. Following the decision that the mother was a possible candidate she was visited by a resident pathologist who outlined the research plan and attempted to obtain her consent to be included in it. The cases were then divided alternately into a study and a control group. The women of the study group received intramuscular injections [5 ml (>6,000 mcg anti-Rh_0(D) per dose) in the early cases and 1 ml (>300 mcg per dose) more recently] of the anti-Rh gamma globulin described above, while those in the control group were not treated. In both the study and control groups blood specimens collected from the mothers in EDTA were examined for fetal cells by the Kleihauer technique. These studies were repeated approximately 48 hours after the initial observation. The women were asked to return for follow-up examinations at six weeks, three months and six months postpartum. Blood groups of mother and infant were confirmed and attempts made to detect antibody production in the control group, and to follow the disappearance of the passively acquired anti-Rh in the study group. The patients and their physicians were asked to report the next pregnancy as soon as possible.

During the subsequent pregnancy the mothers were observed at monthly intervals for Rh antibody development and fetal hemorrhage. The postpartum studies described above were repeated on delivery of the second infant. Commercially available screening cells were used for purposes of antibody detection by saline solution, antihuman globulin, and enzyme techniques. In no case was antibody reported unless identification was made with a panel of cells and a reaction pattern characteristic of one or more of the Rh antibodies was demonstrated.

Before the beginning of the investigation the assistance of experts in data processing from the International Business Machines Corporation was sought and, with their help, report forms were devised on which all data were recorded. From the outset it was our hope that we should record all bits of information of possible importance and that when comparisons were made at the conclusion of the study we would be comparing like items. We endeavored to eliminate influences of various factors, such as parity, manner of removal of the placenta and immunization history, that may play a role in the development of Rh-sensitization.

The final phase of our investigation related to a double blind study which was limited to women who had large fetal-maternal hemorrhages. In this study gamma globulin preparations were supplied to us by the Ortho Research Foundation under code. These women received either an inert globulin or anti-Rh globulin and at the time of injection it was not known which was being given.

Results

The Rh titers that were observed following the administration of 5 ml of the Rh-immune globulin are presented in Table I. The initial titer was generally about 32. As the passively acquired gamma globulin was degraded, there was a gradual decline of titer with complete disappearance in most patients in six months. As expected, the titers were lower and the disappearance sooner when 1 ml was injected (Table 2). The results of the double blind study are shown in Table 3. From these studies it is apparent that the Rh-immune globulin caused rapid disappearance of the fetal cells while the inert material had no effect. One of 12 women receiving placebo (inert gamma globulin) produced antibody. None of the 12 in

TABLE 1.—*Rh Titers in Patients Injected with 5 ml of Gamma Globulin (Antiglobulin Technique)*

Titers	*48 hours Post Injection*	*6 wk.*	*3 mo.*	*6 mo.*	*7 mo.*	*8 mo.*	*9 mo.*	*10 mo.*
Neg.			2	104	109	109	110	111
1:1			14	5	2	1	1	
1:2		3	40	1				
1:4		9	39					
1:8	1	41	15					
1:16	29	50	1					
1:32	72	14						
1:64	16							
Not Examined		1	3			1		

TABLE 2.—*Rh Titers in Patients Injected with 1 ml of Gamma Globulin (Antiglobulin Technique)*

Titers	*48 hours Post Injection*	*6 wk.*	*3 mo.*	*6 mo.*	*7 mo.*
Neg.		2	82	83	84
1:1	4	43	25	1	
1:2	9	58			
1:4	44	12			
1:8	57	2			
1:16	16				
1:32	1				
Not Examined		5	1		

the study group who received anti-Rh gamma globulin produced antibody.

Table 4 summarizes the results of the attempts to suppress Rh sensitization. Thirty-two of 305 control patients have made anti-Rh while there has been no patient who has been treated in the study group observed to produce Rh antibody. Following delivery of a subsequent pregnancy, 69 mothers who received Rh gamma globulin have been studied and none has produced antibody. In contrast, six of forty in a comparable control group are now immunized.

TABLE 4.—*Data Indicating Prevention of Rh Immunization by Treatment*

TREATED		*CONTROLS*	
Total	*Actively Immunized*	*Total*	*Actively Immunized*
322	0	305	32
	Following Subsequent Delivery		
69	0	40	6

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TABLE 3.—*Results of Double Blind Study of 24 Women Who Had Large Fetal-Maternal Hemorrhage*

			Kleihauer Determination (Cells in 10 minutes)		*Titers*			
	Case No.	*Vial No.*	*24 hr. PP*	*48 hr. PI*	*48 hr.*	*6 wk.*	*3 mo.*	*6 mo.*
Placebo*	389B	161	9	6	0	0	0	0
Rh Gam†	413B	155	33	0	4		0	
Rh Gam	422B	160	54	0	8	2	1	0
Placebo	423B	165	45	66	0	0	0	0
Rh Gam	425B	170	31	0	4	4	1	0
Placebo	432B	173	16	35	0		No follow-up	
Placebo	433B	163	9	6	0	0	2	4
Rh Gam	437B	164	163	0	4	4	0	0
Placebo	443B	151	54	41	0	0	0	0
Rh Gam	445B	153	25	0	4	1	0	0
Placebo	464B	154	18	18	0	0	0	0
Rh Gam	468B	156	20	0	4	2	1	0
Placebo	473B	157	16	16	0	0	0	0
Rh Gam	485B	158	20	0	4	2	1	0
Placebo	487B	159	7	6	0	0	0	0
Rh Gam	489B	162	25	1	8	2	0	0
Rh Gam	513B	166	10	0	8	4	0	0
Placebo	532B	167	19	32	0	0	0	0
Placebo	548B	168	14	16	0	0	0	0
Rh Gam	550B	169	69	0	8	4	1	0
Placebo	561B	171	31	35	0	0	0	0
Rh Gam	582B	172	14	0	8	2	1	0
Rh Gam	584B	174	14	0	8	1	0	0
Placebo	591B	175	32	25	0	0	0	0

*Inert gamma globulin.

†RhoGAM.

PP=postpartum, PI=post-injection.

CASE REPORTS

Hygroton-Induced Myopia

PETER D'ALENA, M.D.
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THE PRESENT CASE is the fifth reported case of transient myopia due to chlorthalidone (Hygroton®) so far as could be determined from a search of the literature.*

A 36-year-old white woman was first seen 17 November 1967 with complaint of blurred vision and swelling of the eyelids. As part of a weight reduction program, she had taken 50 mg of Hygroton® (chlorthalidone) on each of three days, November 10, 13 and 15. During this time she lost 8 pounds.

The symptoms had begun 15 November with severe supraorbital headache which lasted 24 hours and was not relieved by aspirin. The next morning the patient felt ill and remained in bed. During this time she noted pain in both eyes and a decrease in vision for distant objects. Her near vision remained normal.

On physical examination bilateral periorbital edema, conjunctival injection and chemosis were noted. These findings were considered similar to those seen in trichinosis and thyroid disease. Blood pressure was 120/80 mm of mercury, and the pulse 72 beats per minute and regular. Body weight was 206 pounds.

The patient had had viral pericarditis in April 1967, and she was receiving iron therapy for iron deficiency anemia secondary to gastrointestinal bleeding. Thyroid evaluation done seven months previously was within normal limits. A hemogram done three weeks before the present episode was normal. The patient said she had received sulphonamide drugs in the past without untoward effects.

Visual acuity with glasses was 20/200 in the right and 20/80 in the left eye. Her glasses contained only a small astigmatic correction. With a —3.00 D (diopter) sphere in the right and a —2.75 D sphere in the left eye, her visual acuity was 20/25 and 20/20 respectively. There was slight bilateral periorbital edema. Slit-lamp examination revealed moderate chemosis and conjunctival injection in both eyes. Near the limbus of the right cornea, at 9 o'clock, was a 1 mm shallow ulcer (dellen). Similar ulcers were present at 3 o'clock and at 9 o'clock of the left corneal limbus. Since the anterior chambers appeared shallow, the pupils were not dilated. No abnormality was observed on fundus examination, and intraocular pressure was normal. Orbital resistance was felt to be slightly increased in both eyes.

The patient was told to discontinue the Hygroton and to return in three days. At that time visual acuity (without glasses) was 20/25+ in each eye. Examination revealed minimal chemosis and conjunctival injection. The patient said that her vision continued to worsen for two days after she discontinued Hygroton but that the next day her vision had returned to normal.

A week later, visual acuity with glasses was 20/20 in each eye. Gonioscopy showed an open angle in both eyes. In the right eye, a small iris cyst was present at 9 o'clock. This cyst was the reason the anterior chamber appeared shallow on the slit lamp examination.

Discussion

Other cases of transient myopia due to Hygroton have been reported. Michaelson[1] reported the case of a 41-year-old woman who experienced decreased vision six hours after taking one tablet of the drug. The acuity was corrected with a —3.75 D sphere in each eye. The drug was discontinued and visual acuity was normal three days later.

Submitted 20 June 1968.

Reprint requests to: San Jose Medical Research Foundation, 45 South 17th Street, San Jose 95112 (Dr. D'Alena).

*Dr. Abraham Mizrahi of Geigy Pharmaceuticals, whose cooperation is here acknowledged, has in his files four cases of Hygroton-associated myopia not reported in the literature. In those cases the patients recovered in about three days without sequela.

Ericson[2] reported two cases of myopia during pregnancy. One patient was a 24-year-old woman in whom myopia developed six hours after she took one tablet of Hygroton. This was corrected by —3.00 D sphere in the right eye and —2.50 D sphere in the left eye. Bilateral macular edema was also noted. Use of the drug was stopped and vision was normal two days later. When the drug was given again, three months after parturition, no eye symptoms occurred. In the second case, that of a 28-year-old woman, myopia of —4.25 D in the right eye and —4.50 D in the left eye developed eight hours after ingestion of one tablet of Hygroton. No retinal edema was present. The patient took no more of the drug and vision was normal three days later. A few weeks later, while the patient was still pregnant, two tablets of Hygroton in divided doses produced myopia of —1.50 D in each eye. This cleared in three days after cessation of therapy.

Pallin and Ericson[3] did ultrasound determinations on a 45-year-old policeman who noted poor vision seven hours after taking a second tablet of Hygroton. A week earlier he had experienced severe nausea, vomiting and diarrhea five hours after one tablet of Hygroton but his vision had not been impaired at that time. The second episode was also accompanied by similar gastrointestinal disturbances in addition to poor vision and a pruritic rash. The gastrointestinal symptoms and rash cleared in 24 hours. Two days after the second Hygroton tablet was ingested the visual acuity was correctable to 20/20 with a —2.50 D sphere in each eye. The next day, after discontinuance of the drug, eye findings were the same. Ultrasound studies, one done at that time and another three weeks later, showed that the lens thickness was greater during the myopic phase.

The mechanism for the transient myopia produced by Hygroton, a heterocyclic sulfonamide, is unknown. Pallin and Ericson[3] expressed belief that certain features of the case they reported pointed to an allergic reaction. In the case reported herein, the periorbital edema, chemosis and conjunctivitis can also be interpreted as being consistent with allergic reaction. Mattson[4] explained the transient myopia occurring with sulphonamide drugs as due to an allergic edema of the ciliary body. This edema would produce myopia by relaxing the lens zonules. Swelling of the eyelids,[5] chemosis[5] and conjunctivitis[6] have also been associated with use of other sulfa drugs. Ericson[2] thought the myopia could be the result of a change in the salt and water content of the lens, and that pregnant patients are more susceptible to the change.

Other drugs which have been reported to produce transient myopia include neoarsphenamine,[7] acetazolamide (Diamox),[8] hydrochlorthiazide (Hydro-Diuril),[9] and tetracyclines.[10]

The signs and symptoms caused by Hygroton, although alarming, disappear completely following discontinuance of the drug.

Summary

A 36-year-old woman had conjunctivitis, chemosis, periorbital edema and myopia following ingestion of three tablets of Hygroton (50 mg). These signs disappeared within one week following discontinuance of the drug.

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Hepatitis and Aplastic Anemia

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WHILE HEPATITIS is occasionally complicated by hematological problems, for the most part these problems are of no great moment. They may consist of hemolytic anemia, leukopenia and thrombocytopenia. Usually recovery occurs spontaneously as hepatitis abates. In the past several years there has been an occasional report of a much more serious complication, that of aplastic anemia following hepatitis. Most of the reports have been in the European literature, with only a few in this country. The purpose of this paper is to report an incident of hepatitis followed by a fatal course of aplastic anemia.

Submitted, revised, 9 January 1969.

Reprint requests to: Parkwood Community Hospital, 7011 Shoup Avenue, Canoga Park 91304.

Report of a Case

An 18-year-old male Caucasian was admitted to Parkwood Community Hospital on 8 May 1967 with chief complaint of fatigue, lethargy, anorexia and nausea. He had been well until, a week before admission, he began to experience fatigue and headaches. A physician who examined him at that time noted enlarged cervical lymph nodes and weakness. The patient had noted neither purpura nor easy bruising. He complained of some irritation of the throat but blood cell counts and heterophil titers were within normal limits.

The patient had been completely well until the onset of these symptoms, except for a traumatic accident to his teeth several weeks before they began. He had not taken any drugs before the onset of symptoms and, so far as he knew, he had not been exposed to any noxious substances or radiation. There had been no loss of weight and no history of pruritus but the patient had noted darkening of the urine. During the week before admission he had been given penicillin and the pharyngitis seemed to improve, although fatigue and weakness continued. By the time he was admitted to the hospital, most of the lymph node enlargement had receded and appetite had improved somewhat. On questioning, the patient said he had not had dysuria, urinary frequency, joint pain or chest pain.

At the time of admission to hospital, vital signs were normal and the patient appeared not to be in distress. There was questionable icterus of the conjunctivae. Neither ecchymosis nor purpura was present but there was a mild pustule-like rash over the hands which was non-pruritic and non-erythemic. The lungs were clear to auscultation and percussion, no cardiac murmurs were heard and the heart appeared to be of normal size. The edge of the liver was palpated 1 cm below the right costal margin and was slightly tender. The spleen was not palpable. The abdomen was not distended and no abnormality of bowel sounds was noted. Preceding and during his entire hospital stay the patient remained afebrile.

The hemoglobin on admission was 15 gm per 100 ml and the hematocrit was 47. Leukocyte numbered 4,900 per cu mm with 65 percent neutrophils, 28 percent lymphocytes, 5 percent monocytes and 2 percent eosinophils. Platelets appeared normal on the smear. Some of the lymphocytes showed atypical changes. Anti-streptolysin O (ASO) titer was 125 units. Prothrombin time was 15 seconds (control 14 seconds). Results of urinalysis and C reactive protein determination were within normal limits. Alkaline phosphatase was 4.0 units (normal 1 to 3.5). Alpha hemolytic streptococcus grew on a culture of material from the throat. The total bilirubin was 4.6 mg per 100 ml, direct 2.4 mg and indirect 2.2 mg. Serum glutamic pyruvic transaminase (SGPT) was 860 units, serum glutamic oxalacetic transaminase (SGOT) 100 units and lactic dehydrogenase (LDH) 790 units. Total serum protein was 6.7 gm per 100 ml with an albumin-globulin ratio of 4.0 to 2.7. The heterophil was negative. Creatinine content was 1.1 mg per 100 ml. Two-hour post-prandial blood sugar was 110 mg per 100 ml and blood urea nitrogen (BUN) 10 mg per 100 ml. Urobilinogen content of a 24-hour specimen of urine was 6.3 mg per 100 ml (normal 0-4 mg).

On 11 May 1967, three days after the patient was admitted, hemoglobin was 16.3 gm per 100 ml, the hematocrit 50 and leukocytes 4,400 per cu mm, with 11 percent banded and 35 percent segmented forms, 47 percent lymphocytes, 1 percent monocytes, 3 percent eosinophils and 3 percent basophils. Ten percent of the lymphocytes were atypical. Total bilirubin was 3.2 mg per 100 ml, with direct 1.2 and indirect 2.0 mg. SGPT was 950 units. An x-ray film of the chest was within normal limits.

The patient continued to do well and he was sent home for further care. On 18 May 1967, total bilirubin was 1.0 mg per 100 ml, with direct of 0.3 and indirect of 0.7 mg, and SGPT was 400 units. Five days later total bilirubin was 1.8 with a direct of 0.4 and indirect of 1.4 mg, and SGPT was 310 units. The patient continued to do well. His appetite increased, he was no longer weak and he was able to carry on normal functions.

On 1 June 1967 the patient was relatively asymptomatic. Hemoglobin was 14.2 gm per 100 ml, and hematocrit 44. Leukocytes numbered 4,800 per cu mm, with 4 percent banded, 60 percent neutrophils, 35 percent lymphocytes and 1 percent monocytes. Total bilirubin was 1.9 mg per 100 ml, with direct of 0.4 and indirect of 1.5. SGPT was 102 units.

On 8 June 1967 the patient began to notice a petechial rash on the wrists, hands and ankles. He had a low grade fever and began to feel somewhat weak. The rash persisted and more petechia and ecchymosis began to appear. On 13 June 1967, the patient was readmitted to the hospital. At examination he appeared well-developed and well-nourished. Vital signs were normal. The conjunctiva appeared somewhat icteric and pale. There were ecchymotic and petechial areas on the soft and hard palate and multiple areas of ecchymosis on oral mucosa and lips. On examination of the gums gingival hyperplasia, tenderness to palpation and easy bruising were noted. A fundoscopic examination revealed no hemorrhages or exudates. The lungs were clear to auscultation and percussion. Multiple petechiae were noted at the ankles and on the upper dorsum of the feet. There appeared to be resolving ecchymotic areas of the lumbosacral area, and the anterior tibial area showed signs of recent bruising and ecchymosis. The spleen and liver were not palpable. The remainder of the physical examination was within normal limits.

Hemoglobin was 11.2 gm per 100 ml and the hematocrit was 30. Leukocytes numbered 1,000 per cu mm with 66 percent lymphocytes and 34 percent segmented forms. There were 50,000 platelets per cu mm and there were no reticulocytes. SGPT was 15 units and the alkaline phosphatase was within normal limits. Total bilirubin was 3.1 mg per 100 ml, with direct 0.1 mg and indirect 3.0 mg. Total protein, albumin-globulin ratio and thymol turbidity were all within normal limits. Partial thromboplastin time was 89 seconds (normal 70 to 150) and prothrombin time 14 seconds (control 14 seconds). Results of direct and indirect Coombs' tests were negative. LDH was 240 units and BUN was 12 mg per 100 ml. Uric acid was 7 mg per 100 ml. Results of urinalysis were within normal limits.

The patient was afebrile and remained so during the hospital stay. Bone marrow aspiration was attempted but no material was withdrawn. A Vim-Silverman biopsy of the marrow was then performed and pronounced hypoplasia, with very few marrow elements present, was noted (Figure 1). No criteria of leukemia were present. On 14 June 1967, serum iron was 85 mg per 100 ml (normal 65 to 150) and iron-binding capacity was 420 mg per 100 ml (normal 255 to 419). Total bilirubin was 3.8 mg per 100 ml with direct of 1.3 mg and indirect of 2.5 mg. Culture of material from the throat grew hemolytic staphylococcus aureus. There was no growth on cultures of blood.

Antibiotic therapy was begun. On 15 June 1967, hemoglobin was 9.2 gm per 100 ml, hematocrit 26, and leukocytes 800 per cu mm with 4 percent band forms, 4 percent neutrophiles, 89 percent lymphocytes and 3 percent eosinophils. There were 30,000 platelets per cu mm. Haptoglobins were 37 mg per 100 ml (normal 40 to 170). Serum protein electrophoresis revealed a total protein of 7.5 gm per 100 ml, with albumin 5.3, globulins 2.2, alpha 1 globulins 3.6 percent, alpha 2 globulins 7.5 percent, beta globulins 6.5 percent of the total and gamma globulins 10 percent of total (normal 9 to 22). Steroids were added to the regimen and the patient remained afebrile and in no apparent distress.

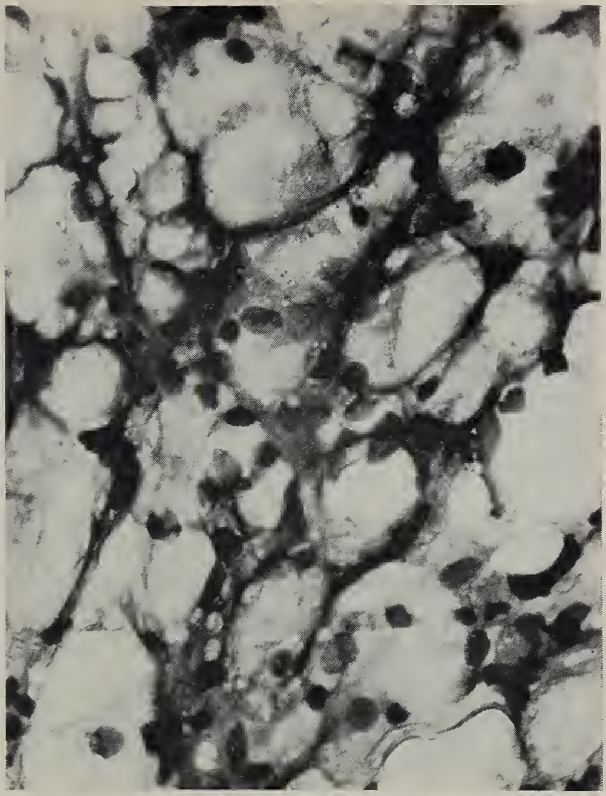

Figure 1.—Section of bone marrow showing absence of myeloid and eythroid elements (× 500).

On 16 June 1967, the patient was transferred to UCLA Medical Center for further care. There infusions of fresh platelets and whole blood were given, and testosterone and steroid therapy were begun. Bone marrow studies still showed pronounced hypoplasia and the clinical status of the patient did not improve. He remained afebrile. Antibiotic therapy for the throat infections was continued, and as before blood cultures continued to show no growth of organisms.

The patient was discharged from hospital 23 June 1967, to be followed as an outpatient. Forty-eight hours later he was readmitted with a high fever and with increased bleeding tendencies and multiple bruises. The clinical course from then on was one of continued deterioration, despite the use of high doses of steroids, antibiotics, testosterone

TABLE 1.—*Hematologic and Enzyme Values in a Case of Hepatitis and Aplastic Anemia*

Date	*Hemaglobin (gm per 100 ml)*	*Leukocytes (per cu mm)*	*Hematocrit*	*Platelets*	*SGPT*
5- 8	15.9	4,900	47	Normal (smear)	860
5-11	16.3	4,400	50	Normal (smear)	950
6- 1	14.2	4,800	41	Normal (smear)	102
6-13	11.2	1,000	30	50,000 cu mm	15
6-15	9.2	800	26	30,000 cu mm	—
7-11	—	600	22	2,000 cu mm	—

and platelet and blood transfusions. On 18 July 1967 the patient died. Autopsy was not done. Table 1 summarizes the hematological and enzyme values.

Discussion

In 1962 Deller and coworkers[1] presented a case of fatal pancytopenia associated with viral hepatitis. Three years later Levy and associates reported five cases of fatal aplastic anemia following hepatitis.[2] Up to the time of the reports by these two groups, accounts of cases of pancytopenia and aplastic anemia appeared sporadically in the European literature. Lorenz and Quaiser[3] and later Kosan[4] reported cases which are almost identical to those cases reported in American journals.[1,2,5] Rubin and coworkers[6] recently presented ten cases and reports have appeared from time to time in the British medical journals.[7] The clinical course and progress in all the cases reported, including the one herein, seem to point to more than a coincidental association between hepatitis and aplastic anemia. The temporal and clinical relationships in the present case closely resemble those noted in other cases, especially those of Rubin.[6] In most cases the hepatitis is resolved, both clinically and cytologically, by the time pancytopenia develops. Most patients are males and most die.

It is well known, of course, that the hemolytic anemia of thrombocytopenia purpura of leukopenia are all hematological complications of hepatitis. However, pancytopenia with severe aplastic anemia seems to be a rather unusual occurrence.

If a causal association does exist, how can the mechanism of this hematological catastrophe be best explained? Is the virus that causes the hepatitis an agent which can cause severe hematological damage? Or does the hepatitis itself produce some metabolic product which damages the bone marrow? It would appear that the latter question is less to the point than the former, since hepatic function usually is adequate by the time pancytopenia develops.

It is known that viral infections may depress one or all three elements of the peripheral blood. Hammon and Enders[8] showed that the virus of malignant leukopenia caused bone marrow aplasia in cats. In addition, Lawrence's[9] work also revealed that pronounced agranulocytosis may occur from viral infection. Evidence indicating that viruses containing ribonucleic acid may cause pancytopenia was observed in cases of Dengue fever.[10] However, hepatitis has not been noted to be a clinical concomitant in these cases. In addition, temporary pancytopenia has been reported in cases of congenital rubella syndrome, and myxoviruses have been associated clinically with leukopenia or thrombocytopenia.

Since the virus of infectious hepatitis is pantropic,[11] it is possible that the aplastic anemia seen in these cases is the ultimate expression of the leukopenia that is so commonly found in cases of infectious hepatitis.

This association of hepatitis and aplastic anemia may explain some of the cases of idiopathic aplastic anemia, since many of them may have been preceded by unrecognized or subclinical cases of hepatitis.

Summary

A case of fatal aplastic anemia following an episode of hepatitis is presented. The temporal and spatial relationships of this case follow closely the cases previously reported.

The case is presented as another documentation of two diseases which may be related by more than coincidence.

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Medical Progress

Current Status of the Management of Patients with Endocrine-Sensitive Tumors

Part II—Carcinoma of the Prostate, Endometrium, Thyroid, Kidney and Miscellaneous Tumors

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CARCINOMA OF THE prostate comprises approximately 6 percent of all cancers and 11 percent of all malignant neoplasms in men. The mortality rate for prostatic carcinoma is 13 per 100,000, and among men it ranks third behind bronchogenic and colorectal cancer. It is estimated that approximately 1,500 men will die of this malignant disease in California in 1969.[35] The disease rarely occurs in men under 50, but the incidence steadily rises with each decade of life and in the ninth decade it approaches 90 percent.[7] Adenocarcinoma of the prostate, although demonstrating great variability in its growth rate, tends to exert its deleterious effects upon the parent organism relatively slowly over a period of several years, despite the fact that extension beyond the prostate is commonly noted at the time of original diagnosis. The overall relative five-year survival rate in California currently approximates 55 percent.[69]

Patients presenting with carcinoma of the prostate are usually categorized into one of four stages. Stages I and II will be combined for the purpose of this review and include all patients in whom the neoplasm, upon complete clinical, laboratory and radiological examination, apparently is confined to the prostate gland. Stage III indicates spread of the tumor beyond the capsule of the gland, but with no radiological or chemical evidence—specifically, elevation of the serum prostatic acid phosphatase—of metastatic spread. Patients with demonstrated metastatic disease are classified as Stage IV. In one large series the numbers of patients categorized in the various stages were as follows: Stages I and II, 13 percent; Stage III, 48 percent; Stage IV, 39 percent.[3]

The classical primary curative treatment has been radical prostatovesiculectomy. More recently, both external and interstitial x-ray therapy, given alone or in combination with surgical or hormonal therapy, have also been utilized with promising results.[5,32,34] Reported five-year survival rates for patients treated with radical surgery vary from 35 to 78 percent.[53,54,89,98] Complications of radical excision include a high incidence of impotence and varying degrees of incontinence.[4] Unfortunately, 90 percent of the patients with carcinoma of the prostate are not suitable candidates for curative treatment by surgical means. For almost 30 years, since the original pioneering efforts of Huggins and Herbst,[45,46,50,52] various programs of endocrine therapy have been employed for the treatment of these patients. These programs include orchiectomy, estrogen administration, adrenalectomy, pituitary ablation, and corticosteroid therapy utilized alone or in various combinations.

The therapeutic use of endocrine manipulation of the patient with prostatic carcinoma is based upon the original observation that the adult prostatic epithelium, both in dogs and man, undergoes pronounced atrophy when the normal physiological effect of androgenic hormones is reduced by removal of their sources or by their biological

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inactivation. The neoplastic offspring of the normal prostate cell likewise exhibits this effect in approximately 60 to 70 percent of patients.[50] When circulating biologically active androgens are reduced in patients with androgen-sensitive tumors, the normal prostate shrinks, and the primary neoplasm and its metastatic deposits show a decreased growth rate and frequently regress to a remarkable degree. The rate of regression from endocrine therapy seems to be related, in some respects, to the degree of differentiation of the cancer cells and their content of acid phosphatase. Extreme anaplasia and lack of acid phosphatase are associated with a poor response to endocrine therapy.[91,109] Both castration and bilateral adrenalectomy presumably exert their beneficial effect by reducing the sources of androgens. The anti-cancer effect of estrogen therapy may be explained by one or more of four actions: (1) inhibition of gonadotrophin production with secondary decrease in the secretion of testosterone; (2) direct inhibition of testosterone production by the testes (recent work in Sweden[9] has demonstrated a selective uptake of radioactive diethylstilbestrol in rat testes); (3) neutralization of androgens, possibly by competitive inhibition at the peripheral target organ; and (4) possibly a direct cytotoxic action on the tumor cell.

Hypophysectomy and corticoid therapy destroy or inhibit the function of the anterior pituitary, which in turn decreases the production of adrenal androgens. A common factor in all forms of therapy seems to be a reduction in the levels of biologically active androgens at the tumor site.

Clinical Endocrine Therapy

Hormonal therapy has been utilized as an adjuvant to the curative treatment of Stage I and II carcinoma of the prostate. Estrogen therapy (5 mg of diethylstilbestrol a day) given, following radical prostatectomy, to patients with Stage I and II disease has not improved results over those obtained with surgical treatment alone. In fact, a decrease in the survival has been demonstrated. A study of 299 patients with prostatic carcinoma, Stage I and II, in 14 Veterans Administration hospitals over a seven and one-half year period revealed that the survival rate for the estrogen treated group was 60 percent as compared with 78 percent for those who had prostatectomy alone.[3] In the estrogen treated group there were 36 deaths, two-thirds of which were due to cardiovascular disease and none of which were caused by cancer of the prostate, as compared with 22 deaths in the non-estrogen treated group, only one-third of which could be attributed to cardiovascular disease. However, six patients died of metastatic carcinoma of the prostate in the group who did not receive estrogens. Results of this excellent study strongly support the opinion that adjuvant estrogen therapy decreases the survival rate in patients with carcinoma of the prostate treated by radical operation, due primarily to an increased incidence of lethal cardiovascular disease. At this time the use of estrogens in this fashion appears to be contra-indicated.

Endocrine therapy is usually the primary treatment for Stage III and always for Stage IV disease. Estrogens alone, orchiectomy alone and sometimes a combination of the two utilized concomitantly or sequentially have been the major modes of treatment employed over the past three decades. Survival rates of patients treated in this manner have been reported to vary from 10 to 57 percent, which is a significant improvement over rates reported before 1940, when they varied from zero to 15 percent.[30,76,77] The improved results have been particularly noteworthy in patients with Stage IV disease. However, endocrine therapy for this condition has never been standardized and there has been no unanimity of opinion as to the relative value or specific indications for the utilization of the various methods. Also, estrogen dosage has varied considerably from one to several hundred milligrams of diethylstilbestrol a day or a similar range of dosage for natural and other synthetic estrogens. However, diethylstilbestrol, 5 mg a day, has been the most common agent and dosage employed. Such a dosage produces profound feminizing effects, including atrophy of the testes, softening and shrinkage of the prostate, enlargement of the breasts (which may be painful), change in the texture of the skin, decrease in libido, edema, nausea and, most importantly, probably increased mortality from cardiovascular disease. There is no apparent difference in the anti-cancer efficacy of natural versus synthetic estrogens. The beneficial effects frequently derived from endocrine therapy include increased longevity, objective regression of tumor, gain in body weight, repair of myelophthisic anemia, relief of pain, eudomonia, and reduction in the elevated levels of serum prostatic acid phosphatase.

The most recent and best report of the relative

TABLE 1.—*Five-Year Survival Rates for Patients With Stage III and IV Carcinoma of the Prostate According to Type of Treatment (3)*

Treatment	*Survival Rates (percent)* *Stage III*	*Stage IV*	*Stage III and IV*
Estrogens alone	52	31	43
Orchiectomy alone	56	33	46
Orchiectomy plus estrogens	44	22	35
Placebo only	57	20	40

merits of the various forms of endocrine therapy for patients with Stage II and IV carcinoma of the prostate arose from the well-controlled randomized prospective study previously noted as having been done by the 14 Veterans Administration hospitals mentioned above.[3] Two thousand and seventeen patients were studied for more than seven and a half years, and they were divided into four basic treatment regimens: (1) estrogens alone; (2) orchiectomy with or without placebo; (3) orchiectomy plus estrogens, and (4) placebo alone. The five-year survival data presented in Table 1 reveal that primary placebo treatment or orchiectomy alone yielded the best results in patients with Stage III disease; whereas, orchiectomy alone or estrogen alone produced the best results in patients with Stage IV disease. Combination of orchiectomy and estrogens yielded the poorest results. A most striking finding was that the placebo group did so well, particularly those with Stage III disease. However, symptomatic relief was noted in a majority of patients receiving endocrine therapy. Also, among patients in the placebo group who were later started on an active endocrine program, 60 percent showed arrest of the progress of disease, with 40 percent showing definite objective evidence of tumor regression. The investigators who made the report drew the conclusion that endocrine therapy should be withheld until the patient is symptomatic and further, that orchiectomy or stilbestrol alone should be utilized rather than combination therapy. In retrospective studies Flocks[33] and Emmett[30] drew similar conclusions, reporting that overall results were improved if estrogen therapy was delayed until the patient was symptomatic. This was particularly true in patients with well-differentiated lesions.

As in the group of patients with Stage I and II disease, it was noted in the Veterans Administration hospitals study that there was a somewhat higher incidence of death due to cardiovascular disease among the patients with advanced stages who were treated with estrogens. In the estrogen-treated groups the number of deaths due to prostatic cancer was less, but the proportion of deaths due to other causes, particularly cardiovascular disease, was higher than that noted in the non-estrogen treated groups. This data is summarized in Table 2. It appears from this study that the use of estrogens tends to reduce the mortality and morbidity due to prostatic carcinoma but increases the number of deaths due to cardiovascular and other causes, and the latter result more than offsets its beneficial anti-cancer effect in the asymptomatic patient. These findings plus the five-year survival figures further strengthen the contention, advanced by the authors of the report, that estrogen therapy should be reserved for patients who have symptomatic disease. The Veterans Administration report, however, fails to clarify whether the patients in the different treatment regimens received comparable total patient management. It is well known that estrogen therapy, in the dosages usually employed for these patients, often induces significant sodium and water retention and aggravates existing cardiovascular disease. However, careful management of these patients with diuretic, anti-hypertensive and cardiogenic drugs and dietary therapy may decidedly lessen this aggravation.

The Veterans Administration medical program is primarily a hospital in-patient effort without attempting to provide general medical out-patient care. In view of this doubt about out-patient general medical care, it is possible that some patients on prolonged estrogen therapy received only specialized urological out-patient care and did not always obtain optimal management of their cardiovascular disease. This factor may have contributed to the high mortality rate.

TABLE 2.—*Cause of Death in Patients With Stage III and IV Prostatic Carcinoma According to Type of Treatment (3)*

Treatment	*Patients*	*Total Deaths*		*Cancer of Prostate*		*Cause of Death* *Cerebral-Vascular Disease*		*Other Disease*	
		No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Estrogens or estrogens plus orchiectomy	949	423	45	132	31	164	39	127	30
Orchiectomy alone	472	195	41	82	42	62	32	51	26
Placebo	484	211	44	102	48	62	30	47	22
Orchiectomy plus placebo	956	406	43	182	45	124	31	98	24

Following cessation of response or lack of original response to castration or estrogen treatment, adrenalectomy has been utilized by a few clinicians with fair results, as manifested primarily by some subjective improvement.[51] It undoubtedly deserves further clinical trial. Likewise hypophysectomy has been done in a small number of cases, with encouraging results.[90] Corticoids also have proved helpful, as in carcinoma of the breast, particularly for the management of pre-terminal patients.[105] Prout and Brewer[83] reported a favorable subjective response in approximately 50 percent of patients who were treated with testosterone, 25 mg daily or 100 mg three times a week. One patient may have had a true remission. The beneficial subjective response was probably related to the anabolic action of testosterone.

Studies aimed at correlating hormone excretion levels with the incidence of prostatic carcinoma or as aids in predicting response to therapy have not been of any significant help. However, response has frequently been correlated with a fall in 17-keto and 17 ketogenic steroids after the initiation of therapy. The initial fall is frequently followed by a slow rise to near normal levels over a period of many months.[20,21] Recent studies by Stern and coworkers[95] suggested that the patients with carcinoma of the prostate differ from matched normal controls in that they tend to excrete less androsterone but greater amounts of gonadotrophin and estriol.

In summary, alteration of the endocrine "environment" of patients with advanced or metastatic carcinoma of the prostate, aimed at reducing the biological activity of androgens, may produce objective evidence of regression of the neoplastic tissue and clinical improvement in a majority of cases. However, the potentially serious hazards of estrogen therapy in particular and the lack of a demonstrable increase in survival, argue against the use of endocrine therapy prophylactically and suggest that such therapy should be restricted to patients with symptomatic metastatic disease, at least until further carefully controlled clinical investigations provide more definitive information.

Carcinoma of the Endometrium

The role of sex steroids in the development of carcinoma of the endometrium has been the subject of considerable investigation over the past 30 years. "In predisposed individuals, the unopposed action of estrogenic substances for considerable periods of time will result . . . eventually in carcinoma," is an expression of current opinion.[94] Four major areas of investigation which support this point of view include studies of: (1) premenopausal women with carcinoma of the endometrium; (2) women with estrogen-secreting tumors; (3) the relationship of endometrial hyperplasia to carcinoma, and (4) experimental models of endometrial cancer.

Although endometrial carcinoma usually occurs in postmenopausal women, one patient in twenty will be less than 40 years of age when the disease is diagnosed. In this group of patients Peterson[82] found that 81 percent gave a history of either amenorrhea or significant menstrual disorders for at least two years before the diagnosis of corpus cancer was made. Low fertility and a very high incidence of obesity were also noted in this group. It would appear that a majority of premenopausal women with endometrial cancer have anovulatory ovarian function and thus are exposed to prolonged estrogen stimulation without the modifying effect of progesterone.

The increased incidence of carcinoma of the endometrium among patients with granulosa and theca cell tumors of the ovary tends to support the concept that estrogens may be actively involved in the carcinogenic process. These tumors generally secrete estrogens, hyperfeminize the patient and induce hyperplasia of the endometrium. The unusually high incidence of carcinoma of the endometrium reported in these patients (ranging from 3 to 27 percent[2]) is extensively documented in the literature. Larson[66] compiled reports of 919 cases of granulosa cell, theca cell, and other feminizing tumors of the ovary from the English literature and found an overall coincidence of carcinoma of the endometrium in 44 cases (4.8 percent). In the 291 women who were postmenopausal, 30 (10.3 percent) had endometrial carcinoma. These figures greatly exceed the incidence of corpus cancer in the general female population of 12 per 100,000 (0.012 percent).[63]

Hyperplastic changes of the uterine mucosa, including adenomata, cystic hyperplasia and anaplasia, are caused by prolonged estrogen stimulation without progesterone. This is frequently seen clinically in the anovulatory situation. It also occurs after exogenous estrogen administration.[37,64] These endometrial changes appear to be related to endometrial carcinoma. Hertig and Sommers[48] studied 32 patients who had endometrial biopsy performed one to twenty-three years before the diagnosis of carcinoma was made. In seven cases in which biopsy was done fifteen to twenty-three years before carcinoma developed, no endometrial abnormalities were present. In cases in which biopsy was done six to thirteen years before malignant change developed, cystic hyperplasia and endometrial polyps were frequently found, while in specimens procured within five years of the onset of malignant change, adenomatous hyperplasia, anaplasia and carcinoma in situ were commonly noted. Hertig and Sommers suggested that there is histologic progression from endometrial polyps to cystic hyperplasia, adenomatous hyperplasia, anaplasia, carcinoma in situ, and finally to invasive carcinoma. This progression takes place over several years. None of these pathological processes, however, necessarily progresses to the next one, and endocrine modification, particularly through decreasing estrogen stimulation, increasing progesterone levels, or pregnancy, may result in regression of the changes to normal.[62,65]

A prospective study by Gusberg and Kaplan[39] supported the above concept. Sixty-eight patients who had histological evidence of adenomatous hyperplasia on curettage for dysfunctional bleeding were followed for more than one year. In eight of them (12 percent) adenocarcinoma of the endometrium developed. The control group consisted of 202 women of the same age and complaint (dysfunctional bleeding) in whom hyperplasia was not found on curettage. In only one (0.5 percent) of the control patients did carcinoma develop in a similar follow-up period. On the basis of this study the investigators considered adenomatous hyperplasia to be endometrial carcinoma, Stage 0. Likewise Wentz[108] reviewed the course of 107 patients with an initial diagnosis of adenomatous or atypical hyperplasia and found that carcinoma eventually developed in seven of them (6.5 percent). In 37 percent of patients who required subsequent procedures because of continuing symptoms, uterine cancer ultimately developed. The interval between the original diagnosis of hyperplasia and the discovery of carcinoma varied from one to four years.

Experimental models in rabbits, the only animal other than man known to have spontaneous development of cancer of the uterine corpus, also implicate estrogens as important etiological agents. By administering estrogens, Meissner and Sommers[75] produced carcinoma of the endometrium in 45 percent of tested rabbits. There was also a high incidence of endometrial hyperplasia in the experimental animals. Griffith and coworkers[36] produced corpus cancer in rabbits by placing a carcinogen (3-methyl-cholanthrene) soaked string in the uterus. If oophorectomy was performed simultaneously with the insertion of the carcinogen, the incidence of malignant disease was sharply reduced. These findings were interpreted as indicating that reduced endogenous estrogen secretion inhibited the action of the primary carcinogenic agent and protected the host from development of the neoplastic change. This supports the concept that the estrogen molecule in certain situations is, in effect, a co-carcinogen.

In contrast to the above findings, there are clinical observations which tend to minimize the probable etiological role of estrogens in endometrial malignant disease. No control studies are available which document an association of exogenous estrogen therapy with an increased risk of carcinoma of the endometrium.[38,63] The vaginal cytology of patients with corpus cancer does not differ from normal controls with regard to estrogen activity.[29] Also, in women endometrial carcinoma can develop many years after castration.[22] However, these latter observations do not absolutely rule out estrogens as playing a significant role in the induction of human endometrial carcinoma. All the studies taken together tend to emphasize that it is probably not the amount of estrogen that seems to be important in fostering hyperplastic and neoplastic endometrial changes, but rather the prolonged, continuous stimulation of the endometrium without progesterone modification.

What with the suspicion that protracted estrogen stimulation plays a role in the development of endometrial malignant disease, it is not surprising that progesterone, which has a profound modifying effect on the estrogen prepared endometrium, has been investigated as a prophylactic and therapeutic drug in the overall management of patients with uterine cancer. Progestins have the ability to reverse the histological changes of endometrial hyperplasia. Wellenbach and Rakoff,[106] as early as 1953, showed that endometrial hyperplasia that was induced by estrogen administration in hamsters after oophorectomy, would disappear on cessation of therapy, and would revert more rapidly if progesterone were given when the estrogens were stopped. The induction of hyperplasia was actually prevented if progesterone was given concomitantly with estrogen. These studies were extended by Griffith and coworkers.[36] They found that rabbits which had a high incidence of endometrial carcinoma following uterine implantation of a carcinogenic string were protected from the development of this neoplasm by progesterone administration. Progesterone also caused regression of established tumors in these animals.

In 1959 Kistner[62] reported that in humans hyperplastic endometrial glands may undergo regression and actively growing stroma may be converted to decidua by the action of potent progestins. By 1965 Kistner's series had risen to 23 patients with cystic or adenomatous hyperplasia and eight patients with carcinoma in situ, all treated with progestins.[65] In a majority of patients endometrial atrophy developed, and some histologic change induced by the drug was observed in all of them. Most of these patients were managed without hysterectomy, and in no case had invasive carcinoma developed although follow-up at the time of report was generally less than five years. This experience has been confirmed by other investigators. Wentz[107,108] reported 54 cases of adenomatous and atypical endometrial hyperplasia in which repeated biopsy over periods of observation ranging from one to four years after a six-week course of dimethisterone or megesterol showed only atrophic or normal endometrium.

The first report of the successful use of progestational agents in the treatment of metastatic carcinoma of the endometrium was made by Kelley and Baker[56] in 1960. Since that time they have enlarged their series.[57] Numerous other investigators have achieved similar results, objective regression being noted in 25 to 30 percent of the cases.[1,59,65,99,103,106] The type of patient most likely to respond is one with a slow growing, well-differentiated adenocarcinoma who has had a long hiatus between the original treatment and the recurrence of tumor.[58,59] The site of recurrence also affects the chance for response. In a series of 165 patients collected from the literature, Kelley and Baker[58] found the following response rate: pulmonary plus osseous, 54 percent; local, 35 percent; pulmonary, 31 percent; abdominal, 24 percent; osseous, 14 percent; and miscellaneous, 38 percent. In patients who experienced a response, previously irradiated tumor deposits responded less well than malignant areas that had not been so treated.[59] A favorable response usually becomes evident within three months of therapy and can be expected to last approximately 16 to 18 months. One case had been in remission for four and a half years at the time of report.[57]

In addition to reduction in the gross size of the tumor following progestin therapy, histological studies have documented an increased differentiation of the lesion,[103] secretory conversion with decrease in size of glands,[99] and decreased mitosis.[1] Patients with objective regression of tumor had a mean survival of 16 to 22 months in two studies,[59,65] compared with a mean survival of four months in the non-responders. The difference in survival is statistically significant, but as the responding group has generally had slower growing tumors, the degree to which therapy affects survival is not entirely clear. However, along with regression of tumor, definite subjective improvement in general well-being, including relief of pain, weight gain and increased vigor, routinely occur as a response to therapy.

Several progestational drugs have been used with equal success. Some that have been used are 17 hydroxyprogesterone-17-n-caproate (Delalutin®),[57,59,99] medroxyprogesterone acetate (Provera®),[1] 21-dimethyl-ethisterone (Ovin®),[23,65] and medrogestone (Colprone®).[103] Generally very large pharmacological doses have been employed, such as 1,000 to 5,000 mg per week of Delalutin or 500 mg per week of Provera.[65] The drug is discontinued after six to eight weeks if no beneficial effect is detected but is maintained until relapse if a response occurs. Contrary to the experience with most forms of chemical therapy for malignant disease, side effects associated with progestin therapy have been minimal.

Several investigators have reported the use of progestins as an adjuvant preradiation or presurgical treatment of patients with uterine cancer.[65,99,107,110] The usual treatment course consists of three to twelve weeks of hormonal therapy. In the majority of cases, a decrease in the size of the uterus and in the amount of bloody discharge occurred, and it was common to find absence of tumor cells in the curettage specimen after progestational therapy and before radium implantation. Technical difficulties with radium implantation were lessened. In a few cases intracavitary progestins produced similar results.[65,107] A few patients have been treated with Delalutin alone for invasive endometrial carcinoma.[110] If curettage after the hormone had been given revealed no residual tumor, Delalutin was continued. However, there is no information on long term results with this program. It has also been suggested that prophylactic administration of progestins may be of some value in the prevention or delay of recurrence after primary therapy, much in the same way thyroid extract is given after operation to patients with carcinoma of that gland.[65] However, no study has been reported evaluating the results of such prophylactic adjuvant therapy.

The mode of action of progestational agents in carcinoma of the endometrium has not been established. The most convincing evidence supports a direct effect of the hormone on the tumor cells. Dramatic regression has occurred with intracavitary topical medroxyprogesterone acetate.[65] Direct injection of the same drug into perineal metastatic lesions has been reported to bring about decrease in tumor size after the systemic form of the drug produced no beneficial effect.[93] Adenocarcinoma of the endometrium grown in tissue culture has been inhibited by direct application of a potent progestin.[44] An indirect effect mediated via the pituitary gland was suggested by Sherman and Woolf,[92] who found that luteinizing hormone was elevated in patients with carcinoma of the endometrium and that these levels were decreased to normal after treatment with progestational compounds. Varga and Henriksen,[100] however, were unable to duplicate these findings. The possibility that the effectiveness of progestins are due to their metabolic conversion to estrogenic, androgenic or glucocorticoid hormones is very unlikely, since no such conversion has been demonstrated.[1,108]

A fair summary would then be that carcinoma of the endometrium is more likely to develop in a hormone environment resulting in sustained estrogen stimulation of the endometrium without progestational modification. Adenomatous endometrial hyperplasia is a precursor of carcinoma, and reversion to normal or atrophic endometrium usually can be brought about by progestational therapy. Carcinoma of the endometrium whether in its primary or advanced metastatic form will, in approximately one-third of cases, regress on progestin therapy, and this is associated with significant palliation and some evidence of prolonged survival. The mode of action of the progestins is most likely directly on the tumor. Prompt treatment of early endometrial hyperplastic states with progestins, provided follow-up curettage is routinely practiced, may be helpful in reducing the incidence of uterine carcinoma.

Carcinoma of the Thyroid Gland

The possibility that excessive pituitary hormonal stimulation of the thyroid gland may induce thyroid carcinoma is supported by both animal and human studies. Methylthiouracil given to rats inhibits thyroid production, and the resulting increase in thyroid stimulating hormone induces thyroid hyperplasia, adenoma formation and carcinoma with metastatic potential.[42,84]

The controversial postulation that carcinoma of the thyroid in humans is related to increased supply of the thyroid stimulating hormone was reviewed recently by Bucalossi and coworkers.[19] An increased incidence of thyroid malignancy in areas of endemic goiter was found in several studies.[23,104] An increase of the TSH secreting cells of the pituitary was noted in the majority of patients with thyroid carcinoma.[87] The multifocal origin of this malignant disease[10,86] also suggests a systemic factor in its development. Thyroid carcinoma has been shown to take up I^{131}, to produce thyroxin (T_4), and to have this production suppressed by thiouracil, thus confirming that this malignant lesion can, on occasion, retain the hormonal activities of the parent normal thyroid cells.[67] The above mentioned clinical experimental observations suggest that hypothyroidism and elevated TSH production may stimulate tumor growth in the thyroid and the removal of TSH stimulation may suppress it.

Sir Thomas Dunhill is reported to have been the first (1930) to use exogenous thyroid extract to treat patients with metastatic thyroid cancer.[24] He describes three patients in whom the lesions regressed for 17 to 22 years. Others have reported tumor regression after treatment with thyroid extract.[11,12,71] Crile[26] has reported the largest series to date; he treated 19 patients who had metastatic papillary or mixed papillary-follicular tumors with 0.2 to 0.3 gm of dessicated thyroid a day. Twelve of the 19 had objective regression of nodes or of chest lesions or both. The average follow-up was 11 years, and the most impresive finding was that none of the responders showed any evidence of relapse while thyroid extract was continued. The incidence of response was greater in patients under 35 than in older patients: 11 of 14 patients under 35 years of age had regression of tumor, but only one of the five who were more than 35 had a similar response. Thomas[97] reported objective regression of metastatic thyroid cancer in seven of twelve patients so treated. Not all of his patients recovered completely, and deaths related to thyroid neoplasm occurred after temporary remissions had relapsed. Crile made the point that undifferentiated and pure follicular lesions do not respond well.[24] The use of dessicated thyroid as an adjuvant to surgical therapy for patients with carcinoma of the thyroid, with the goal of prolonged suppression of any residual foci of local or metastatic disease has been recommended by many observers.[25,43,74,97] No long term study has proved the effectiveness of this treatment, but Crile[25] reported no recurrence in 35 patients with papillary disease who were observed for four to five years of thyroid medication. This is an improvement over his previous experience of recurrence in 20 percent of cases, mostly within the first year of follow-up.

Bucalossi and coworkers[19] took a more direct approach. They attempted pituitary ablation with Y^{90} implantation in 14 patients with advanced thyroid cancer. Five of the 14 had objective tumor regression for six to twenty-eight months. Eleven patients were evaluated post-implantation for residual pituitary function. Three of four who had complete ablation had good tumor regression while in only two of seven with residual pituitary function was there any objective change in the tumor. All of the tumors which responded were well-differentiated while none of the four undifferentiated tumors showed improvement.

Present evidence suggests that suppressive doses of thyroid extract (0.2 to 0.3 gm a day) may cause regression of many papillary and some follicular carcinomas of the thyroid, and such therapy is an effective weapon in the arsenal for treating this ubiquitous disease. Similar doses of thyroid extract should probably be given to all patients following lobectomy or subtotal thyroidectomy for thyroid adenomata and other hyperplastic conditions. Such therapy may prevent the future development of carcinoma in the residual gland.

Carcinoma of the Kidney

Only recently suspicion has been raised that renal carcinoma is an endocrine-sensitive tumor. In 1944 Vasquez-Lopez[102] noted a tumor of the kidney in a male hamster which had been treated with estradiol benzoate during a study of the effect of estrogens on the pituitary and gonads. Three years later Matthews, Kirkman and Bacon[72] noted that estrogen administration to male hamsters consistently caused renal adenomas and metastatic carcinoma. The tumors thus engendered experimentally have been extensively investigated. A variety of estrogens are capable of inducing renal tumors in hamsters, but this action is inhibited if either progesterone or testosterone is administered simultaneously with them.[60] The protective effect of progesterone is consistent with failure of estrogens to induce renal tumors in mature females. Hormonal manipulations which reduced endogenous progesterone production render female hamsters susceptible to the carcinogenic effect of estrogen.[61]

Estrogen-induced tumors can be transplanted to either male or female hamsters, but only if exogenous estrogen is supplied. After several serial transplants the tumor becomes progressively more autonomous and finally is independent of exogenous estrogen. The effects of hormones on tumor growth vary with the stage of autonomy the tumor has developed. Progesterone has an inhibitory effect on the induction of the primary tumor and on estrogen-dependent transplants, but has no inhibitory effect on the more autonomous transplants.[17] Testosterone inhibits formation of primary tumors, but, once the tumor has formed, its growth is stimulated by male hormone. This is true for both primary and estrogen-dependent tumors,[60] but has no measurable effect on autonomous tumor transplants.[17] Cortisone increased the incidence of primary tumors and the incidence of metastasis in estrogen-dependent transplants, but did not change the growth rate of these tumors.[60] Transplanted tumors which have become independent of estrogen, however, were decidedly inhibited in their growth rate by prednisone.[17] Orchiectomy does not inhibit the induction of renal tumors or transplantation of the estrogen-dependent tumors. The growth of estrogen-independent tumors, however, is decidedly inhibited by this procedure.[16] Adrenalectomy causes a response similar to orchiectomy, but the inhibition is less dramatic.[16]

The effectiveness of certain endocrine manipulations in retarding the growth of experimental renal cancer has led to the use of these measures in advanced hypernephroma in humans. Bloom[14,15] utilized several types of hormone therapy in the treatment of 38 patients with carcinoma of the kidney. Twenty-three of the patients were seriously ill or moribund at the time endocrine treatment was begun. Eight had objective improvement as observed clinically or roentgenographically two to six weeks after the beginning of therapy. Eighteen of the 38 patients had subjective improvement. Two patients seemed to have accelerated growth of the tumor coincident with therapy. Proportionally more men than women had objective regression—six of 21 men, two of seventeen women. The average age of those who responded was ten years greater than of those who did not. Contrary to the experience with tumors of the breast, prostate and endometrium, a prolonged free interval was not associated with response; rather, the reverse seemed to be true. The length of regression varied from two months to greater than three years. Samuels and coworkers[88] recently reported results similar to Bloom's. Objective regression was noted in four of 23 patients and in no case was there accelerated growth during endocrine therapy.

A variety of treatment schedules have been employed. Details of treatment are available in 20 cases treated by Bloom[13] and 23 cases reported by Samuels.[88] Many patients received a second or third drug if there was lack of response or relapse with the first agent. Forty patients received medroxyprogesterone acetate (Provera) with seven remissions, and 21 received testosterone with two remissions, and one of eight patients responded to prednisone. Bloom[14] suggested a treatment plan of medroxyprogesterone acetate, 100 mg three times a day by mouth for six to eight weeks. If there was no response, he then substituted testosterone propionate, 100 mg a day five days a week. For cases in which there was still no response or recurrence developed, he recommended trial with prednisone followed by stilbestrol. Samuels and coworkers differ only in that they prefer a parenteral form of a progestin utilized for at least three months before changing to testosterone. The mean survival of responders in both series was 16 months. Since the expected mean survival with metastatic renal carcinoma is seven months, it would seem that objective response is accompanied by prolongation of survival.[88] Experience with the hormonal therapy for patients with renal cell carcinoma is limited but the early results are sanguinary and justify further clinical and laboratory investigation of the endocrine relationships of this tumor.

Miscellaneous Tumors

There have been numerous reports of a single case or a small series where hormonal therapy was used in a variety of advanced malignant lesions. Occasional objective responses have been reported in patients with the following neoplasms:

Carcinoma of the Ovary:

Androgens have been reported to produce some subjective improvement without objective remission.[8] Decrease in size of a metastatic ovarian lesion coincident with estrogen therapy was noted in one case[47] and with progestational therapy in two cases.[55,101] Ninety percent of cases in one series had no decrease in tumor size, however.[101] Several patients had a decrease in ascites or pleural effusions, which may be related to the known diuretic effect of progestins.[27]

Squamous Carcinoma of the Cervix:

Progestational agents have been administered to patients with carcinoma of the cervix without evidence of any change in progression of the tumor[6,49,55] although some patients required less narcotics and had an increased sense of well-being. In two cases, in which hypogastric artery ligation was being considered because of bleeding from the tumor, improved hemostasis shortly after progestational therapy was begun made the operation unnecessary.[101] A similar result from diethylstilbestrol has been reported.[73,78] Dramatic objective shrinkage or disappearance of the tumor as noted with carcinoma of the endometrium has not been found.

Tumors of the Uterine Musculature:

In one case of leiomyosarcoma of the uterus a decrease in the size of palpable tumor occurred following progesterone therapy.[55] One case of dramatic objective remission in metastatic proliferative stromatosis with medroxyprogesterone acetate has recently been recorded.[81] There has been no reported benefit from progestational therapy in endometrial sarcoma, mixed mesodermal tumors, and choriocarcinoma.[101]

Carcinoma of the Bladder:

In the mid 1940's three patients with papillary carcinoma and one with squamous cell carcinoma of the bladder were reported to have had some decrease in tumor size during estrogen therapy.[40, 41,68] No current reports are available to confirm the value of this therapeutic approach.

Carcinoma of the Seminal Vesicle:

Rodriguez-Kees[85] reported dramatic objective remission of carcinoma of the seminal vesicle in a patient treated with orchiectomy and estrogens. Local lymph node, osseous and pulmonary metastatic disease all involuted. The patient continued to thrive one year later.

Desmoid Tumors:

A lesion similar to these locally recurring connective tissue tumors has been produced in guinea pigs by estrogen administration, and has been prevented by giving progesterone or testosterone.[70] Regression of desmoid tumors in women has been reported associated with puberty,[96] with castration[79] and with menopause.[28] Disappearance of a palpable tumor mass following administration of prednisone has also been reported,[18,80] and so has spontaneous regression without hormonal changes.[31]

The true value of endocrine therapy for patients with malignant diseases of the foregoing "miscellaneous" orders has not been clarified. The routine use of hormonal agents for these patients is not recommended. However, further clinical investigations in well-controlled settings should continue.

Conclusion

Animal studies commonly imply, and clinical observations in humans suggest, that variations from the normal endocrine environment of the host may be a factor of varying importance in the complex inductive process of mammary, endometrial, thyroid, renal and possibly prostatic carcinoma. Changing the abnormal environment associated with the malignant inductive process decreases the incidence of carcinoma in some animal systems and may have an inhibitory effect on the development of human thyroid and endometrial carcinoma. Many more observations are necessary to confirm present concepts and to extend our knowledge of the hormonal factors in tumor induction, but current knowledge already suggests the potential clinical usefulness of detecting these hormonal abnormalities and reversing them when possible.

Established tumors of several endocrine target organs may be dependent, to varying degrees, upon a specific hormonal environment; and the alteration of this environment causes tumor regression and clinical improvement in about 30 to 45 percent of patients treated. Subjective improvement alone, probably due to various metabolic effects of specific hormones (androgens and corticoids in particular), occurs in a few more patients. The most effective therapy has proved to be treatment plans which reduce the biological activity of estrogens in mammary carcinoma, androgens in prostatic neoplasms, and thyroid-stimulating hormone in cancer of the thyroid. They appear to act by depriving the tumor cell of a specific hormone or hormones necessary for continued growth. In addition, some hormones, progestins in particular, may have a direct cytotoxic action. The ideal timing of therapy remains the subject of continued controversy, but current evidence suggests that endocrine treatment should usually be reserved for management of the patient who has evidence of rapidly progressing neoplastic disease or is symptomatic, but before there has been much deterioration of the host. An exception is the prophylatic use of thyroid extract in suppressant doses following surgical excision of hyperplastic and neoplastic thyroid lesions, and perhaps progestins for patients with hyperplastic endometrial changes.

The treatment of patients with incurable carcinoma remains a tremendous challenge to the clinician. Endocrine therapy, both ablative and additive, is a powerful and useful weapon for the management of these patients with endocrine-sensitive tumors. Skillful use of it is difficult and time consuming but frequently very rewarding. The goal should always remain true palliation, which means not only prolongation of survival but, more importantly, real improvement in the quality of that survival.

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SYSTEMIC DISTURBANCES WITH MIGRAINE

"In the common migraine—and we call it common because it is indeed the most frequent—you have multisystemic disturbances; and sometimes the systemic disturbances, the associated symptoms, will outweigh the headache. So this must be looked for in your diagnosis. The headache itself does not have to be unilateral; it may be bilateral . . . from the beginning. The prodroma are not sharply defined . . . visual, sensory, or motor, but visual most commonly. The family history is less dense and the personality profile is less rigid than we see in the classic migraine. So the misdiagnosis of migraine is most often in the common migraine which comprises as many as 80 percent of all migraines. You may get a severe headache or a milder headache with a variety of systemic disturbances, and they should be recognized as such."

—Arnold P. Friedman, M.D., New York City
Extracted from *Audio-Digest Otorhinolaryngology,* Vol. 1, No. 4, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

MEDICAL STAFF CONFERENCE

Changing Drug Patterns in the Haight-Ashbury

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Associate Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. SCHMID:* We have a special subject this morning: Changing drug patterns in the Haight-Ashbury. We have no patient today to present to you, but fortunately we have Dr. David E. Smith to discuss the subject. Dr. Smith is Medical Director of the Haight-Ashbury Medical Clinic, Assistant Clinical Professor at the University of California San Francisco Medical Center, Lecturer in Criminology at the University of California at Berkeley, and Editor of the *Journal of Psychedelic Drugs.*

DR. SMITH: For better or for worse, San Francisco was the "acid"† capital of the world for a long time, and now it has become the "speed"‡ capital of the world.

My presentation on "Changing Drug Patterns in the Haight-Ashbury" will be based on my clinical experience at the Haight-Ashbury Medical Clinic and at San Francisco General Hospital, and on research conducted through the Department of Pharmacology under the direction of Dr. Frederick Meyers entitled "Drug Practices in the Haight-Ashbury Subculture." In reference to the effects of chronic LSD use, I will be presenting some very good work done by Dr. Kay Blacker and his group at Langley Porter Neuropsychiatric Institute in which a group of chronic LSD users was studied in depth.

For those physicians who have had little experience or little understanding of youthful drug abuse, I want to begin by presenting a few basic facts. So many people, particularly in the medical community, focus only on the drug factors. It is quite apparent that in analyzing the drug reaction, drug factors or the agents of drug abuse represent only part of the overall reaction, while personality and group factors represent the other crucial variables.[2] We must realize that a drug interacts with a particular individual who is at the same time interacting with those around him in the immediate drug environment. In addition, group or cultural factors influence his mental set or attitude toward his drug experience. By altering any one of these variables it is possible to alter the acute drug reaction and influence the chronic drug pattern.

In the Haight-Ashbury district of San Francisco, methamphetamine abuse has become the major youthful drug problem. The "speed freak" has replaced or "driven away" the "acid head," and as a result Haight-Ashbury has been converted from an acid subculture to a speed subculture. I will begin this presentation with an appropriate clinical description.

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*Rudi Schmid, M.D., Professor of Medicine.

†"Acid" is the street name for LSD.

‡"Speed" is the street name for methamphetamine.

High-Dose Methamphetamine Abuse: The Speed Cycle

To understand high-dose methamphetamine abuse, one must understand the manner in which it is taken. Like the user of any drug, the "speed freak" has certain motivations and expectations for his drug use. A parallel with alcohol use would familiarize this for the audience. You may have a martini during the week and set as your expectation relaxation. On Friday or Saturday, not having to get up the next morning, you set as your expectation intoxication and have three or four martinis, thus varying the dose to meet your goal. In all cases people have expectations from their drug use. It is important for the physician to attempt to understand these motivations for drug use not only as they bear on acute treatment but also with regard to chronic treatment and intervention of a potentially destructive life-style.

The person who uses high dose methamphetamine is seeking the "flash" or the "rush." In other words, he injects the substance and has a very rapid reaction which he describes as a "full body orgasm." The methamphetamine-induced excitation and agitation that follows is, in a "speed freak," a secondary consideration. He is after the initial phenomenon of the injection. The patient emphasizes that his objective from "shooting" speed is the flash or orgasmic feeling, and that the euphoria or sense of wellbeing is a secondary consideration. Individuals often start on oral methamphetamines and develop a desire for the "high," the excitation of the oral amphetamines. But for various reasons ranging from group pressure to personality problems they find that the intravenous injection of the substance is even more desirable, leading eventually to this distinctive and destructive pattern of drug use.

As you know, methamphetamine interrupts sleep patterns and suppresses appetite. The individual may go on a "speed binge" lasting three or four days in which he "shoots up" from one to ten times a day, always going for the peak experience. He does not eat or sleep during this time. He is in a continual state of hyperexcitement until, for one of various reasons, he decides to terminate this "speed binge." This may occur for several reasons—exhaustion and fatigue, abnormal psychological circumstances that are frightening to him, or inability to obtain the drug.

For whatever reason, the "speed binge" is terminated and we then see the reaction phase of the speed cycle. The reaction phase to the "speed binge" is classically the exhaustion syndrome. The individual often lapses into a deep sleep for periods of from 24 to 48 hours, depending on the duration of the "speed binge"; and upon awakening he may eat ravenously. The management of the exhaustion syndrome is relatively easy, and treatment consists primarily of supportive care. To contrast the speed cycle with the heroin cycle, when the heroin addict is intoxicated he may be sedated or "on the nod," whereas the intoxicated methamphetamine addict is hyperexcitable and agitated. After withdrawal from methamphetamine, a state of exhaustion exists, but in heroin withdrawal a state of excitation predominates. So we have a decided contrast between the intoxication and withdrawal phenomena of these two different drug dependencies.

I have described the action-reaction cycle, but unfortunately many of the amphetamine users do not return to a baseline level of personality function. They have a prolonged subacute phase in which profound depression dominates. Very often the "speed freak" shoots methamphetamine again to treat his depression and another cycle begins. The intensity of the post-speed depression cannot be overemphasized. As one 17-year-old girl said to me when I was attempting to motivate her for therapy, "Without speed I feel so lousy that I'd rather shoot speed and live for one week than live for 40 years without it." Very rapidly a situation of desperation develops in which the patient sees no hope for interruption of this pattern of drug use, and the only feasible therapy is to remove the individual from that drug-using subculture. There is a good institutional program at Mendocino State Hospital and there is a self-help out-patient program in the city of San Francisco directed by the Haight-Ashbury Clinic. But so long as the "speed freak" maintains himself in an area where many other persons are also using the drug, he has a great deal of difficulty resisting the temptation to "go back up" again.

Medical and Psychological Toxicity of High-Dose Methamphetamine Abuse

I would like now to discuss some of the psychological and physical complaints that develop as a result of high-dose methamphetamine use. Last summer we analyzed 310 cases of high-dose methamphetamine abuse seen at the Haight-Ashbury Clinic during a three-month period (June to September 1967).[3] This is an unusually large number of intravenous drug users of this type, and it indicates that methamphetamine abuse has been present for some time. Approximately 40 percent of the patients came to the clinic with physical complaints, 60 percent with psychological complaints. This is important when one views a drug treatment facility as basically a psychiatric facility. The medical facility can very often serve as a contact point to encourage longer term therapy or to motivate the patient for treatment for his psychological problems.

As to the physical complaints, we saw an unusually high incidence of hepatitis, a bewildering array of urticarial reactions, abscesses, respiratory complaints, and acute abdominal complaints. In observing the patients, it became apparent that acute gastrointestinal distress or abdominal cramps are part of the high-dose methamphetamine syndrome. I will not go into detail about the physical complaints, however; I prefer to focus on the types of psychological consequences that develop. These consequences can be divided into five categories:

1. Anxiety reaction
2. Amphetamine psychosis
3. Exhaustion syndrome
4. Prolonged depression
5. Prolonged hallucinosis

The major psychological complaint encountered was the simple acute anxiety reaction. The individual had overdosed and had become acutely anxious, concerned, tremulous, often with tachycardia and somatic concerns. In talking about dosage I must emphasize that virtually all the methamphetamine now available is black market methamphetamine. It is not therapeutic diet pills diverted into an illegal market. It is mainly synthesized by black market laboratories, and therefore an accurate assessment of dosage is difficult to obtain. Although the average therapeutic dose for appetite suppression is 5 to 15 mg, because of the rapid tolerance that develops with this drug, the "speed freak" shoots between one and five grams a day. The tolerance varies so widely among various users, however, that one questions whether this is a physical or a psychological tolerance.[4,6]

The amphetamine psychosis is less common and is associated with three diagnostic characteristics: (1) Visual hallucinations, (2) auditory hallucinations, and (3) a well-defined system of paranoia including ideas of reference.[6] Paranoia is a characteristic part of the reaction and makes treatment difficult because the individual is very concerned about entering a hospital or encountering the police. He feels comfortable only in a street facility and very often even there questions concerning the police arise. As an example, I saw an 18-year-old white man who had been having an amphetamine psychosis. He had a very well-defined system of paranoia in which he felt that the police were after him and that his roommate and he had come to the Medical Clinic for help. Except for this system of paranoia and distracting hallucinations, he was remarkably lucid. During our interview a staff volunteer of the clinic, wearing a black leather jacket, crossed in front of the door. The patient jumped up and said, "I knew it! You're part of the plot!" and tried to run out the door. While restraining the boy, I called the volunteer and indicated that this was a member of the clinic staff who just happened to wear a black leather jacket. He calmed down immediately. The movement in and out of a paranoia delusional system can be very dramatic, and the physician may suddenly become part of that system. If the patient happens to be large or violent, the physician may be in some immediate jeopardy.

In the amphetamine psychosis certainly the major psychochemotherapy is anti-psychotic drugs of the phenothiazine type. For these psychotic reactions the physician must also give serious consideration to getting the patient into a hospital if facilities are available, since the psychotic symptoms often persist. For the anxiety reactions, long-acting sedatives are enough. However, the acute anxiety reaction is self-limiting, and many times the physician tends to overtreat. Transition from the action to reaction phase can be quite dramatic, and the consequences of the anxiety reaction can be easily handled with a supportive, nonthreatening environment and the cautious use of sedative medication.

I have talked about the exhaustion syndrome and the appearance of a tenacious reactive depression. I would also like to mention the phenomenon of prolonged hallucinosis in which the high-dose amphetamine user experiences persistent auditory and visual hallucinations for days and even weeks after the acute reaction has passed. Only a few of those who have an amphetamine psychosis manifest this prolonged reaction, and we are not certain if drug factors or personality factors play the major role in this drug-induced thought disorder.[2,4,5,6]

I want to close my discussion of chronic high-dose methamphetamine use by emphasizing the importance of group factors as a major contributor to amphetamine toxicity. In a series of animal experiments we found the LD50 of d-amphetamine to be 100 mg per kg when the drug was administered to white mice housed individually. When the animals were grouped together and the environmental conditions remained constant, the LD50 decreased to 25 mg per kg. In other words, simple aggregation of the animals increased the toxicity of the drug fourfold. In analyzing this phenomenon of aggregate amphetamine toxicity we found a polyphasic mortality curve. The mortality was high at the 25 mg per kg dose and then decreased, so that at 75 mg per kg the drug was less toxic than at 25 mg. It then increased again at 100 mg per kg where a second LD50 appeared. In analyzing this polyphasic mortality curve we found that at the 25 mg per kg dosage, the animals were in a hyperexcitable and agitated state in which the mechanism of death was actually that of one animal killing another. As the drug dose was increased the animals became preconvulsive. The dose was not high enough to cause convulsions (the mechanism of death at 100 mg per kg), but the animals were so disorganized that they could not mobilize directive attacks at one another.[5]

The Haight-Ashbury now has some resemblance to a giant mouse cage in that individuals are taking high-doses of central nervous system stimulants and interacting very often in a destructive fashion. It has become quite apparent that just taking the drug in the high density population situation increases the toxicity. It is very important for the physician to be aware of the phenomenon of aggregate toxicity. Treatment of any central nervous system stimulant reaction should put great emphasis on a quiet, supportive, nonthreatening environment. A caustic statement by the physician or a nurse bursting into the treatment room would constitute poor treatment in this situation. I hope that persons who are treating drug reactions will become aware of the importance of environmental group factors in treating both amphetamine and LSD reactions.

The "Acid Head"

I have discussed a situation in which a person who is chronically using methamphetamine becomes violent, hostile and hyperactive. The chronic LSD user, the "acid head," presents an entirely opposite picture. In our clinic population, individuals who were using methamphetamine chronically were approximately the same age as those who were using LSD chronically. There were significant differences, however, in personality types and socio-economic background between the two groups of drug users. Of greater significance, however, is the fact that the chronic LSD user developed a pattern of thought and behavior which was the antithesis of that described above in the chronic methamphetamine user. Rather than seeking a "flash" or a thrill as did the "speed freak," the chronic LSD user developed a complex set of motivations for his drug use involving self-spychoanalytic, pseudo-religious and creative aspirations.

To understand the chronic effects of LSD, however, one must understand the psycho-pharmacological effects of the drug. To begin with, the individual under the influence of LSD manifests very pronounced perceptual changes. Primarily these changes are illusionary phenomena (for example, objects changing shape and color). On the other hand, one may see the phenomenon of synesthesia in which one sensory phenomenon is translated into another (for example, a record player gives off colored vibrations or an individual smells purple). Teenagers are well aware of the phenomenon of synesthesia and have immortalized it in songs such as "Good Vibrations." The perceptual changes are the most pronounced of the phenomena that one finds, but hallucinatory activity—that is, the actual perception of an object in one's sensory environment without the physical manifestation of that object — is relatively rare with LSD. One also sees decided alterations in symbolic associations with sensory input. For example, an individual may see a red light and become enamored of the hue of the light rather than make the symbolic association that one stops at the red light. Pronounced alterations in ideational functioning also occur. Very often individuals who have taken LSD tend to feel that they have had a universal religious experience in which they have found the answer to life. They develop a rather elaborate philosophical position around this sensory pattern and very often, particularly in the young mind, carry this into their non-drug state. In other words, they do not say, "This is just a drug reaction that gave me this subjective or illusionary experience"; they say, "I've found the answer to life!" If LSD is taken in a psychedelic information environment where other individuals have had the same experience, then the interpretation of psychedelic reality is reinforced. Repeated LSD experiences with friends supporting a positive interpretation of the LSD experience produces some very dramatic psychological changes in the "acid head." I have described this characteristic alteration in the chronic LSD user as the "psychedelic syndrome."[3]

The characteristics of this psychedelic syndrome are, first, a profound belief in non-violence. The "acid head's" rejection of physical aggression is so profound that very often one sees a change in diet to natural, vegetable foods; his rejection of killing is so great that he refuses to eat meat. Another of the significant characteristics of the individual who uses LSD chronically and develops the "psychedelic syndrome" is a belief in *magic*: Mental telepathy, astrology, extrasensory perception, mysticism, and telekinesia are all parts of his belief system. He believes that his mind can communicate and produce changes in his physical environment because his LSD experiences demonstrated this. The "acid head" develops a life-style based in this particular belief system. For example, an "acid head" may not come to work at the Haight-Ashbury Clinic because "the stars are wrong" or "it's impossible for me to interact or work with [some other person] because our signs conflict." Recently there developed a sincere belief that a meteorite was going to hit San Francisco and a large number in the community left town for Colorado.

Medical Significance of the "Psychedelic Syndrome"

What medical significance does the "psychedelic syndrome" have? Persons with "psychedelic syndrome" tend to group together in communal living situations, and it is a combination of chronic LSD usage and the psychedelic community that reinforces behavior of this type. They undergo a profound psychological conversion to belief in an unstructured psychedelic religion.

The medical significance of the "psychedelic syndrome" is vague. In Dr. Kay Blacker's studies[1] at the Langley Porter Institute no classical evidence of organic brain damage was found in chronic LSD users. On the other hand, he found with visually evoked electroencephalographic responses an increase in the number of low intensity visual responses. But in another test sensitive to intellectual disorganization or schizophrenia, the auditory two-toned evoked potential, the group of LSD users showed no abnormality. In other words, as Dr. Blacker pointed out, an alteration in one type of psychological testing which may be characteristic of a schizophrenic process does not imply an alteration in an entirely different type of psychological testing. His assumption is that the chronic LSD user tends to modulate and organize sensory input in a different and unique fashion. In other words, he views the world differently from the nonuser or the casual user of LSD. His subjects had intact and intense interpersonal relationships and could not, using standard nomenclature, be described as schizophrenic—merely as eccentric. The breakdown in interpersonal relationships occurs between the "hip" and the straight community or between the nonpsychedelic and the person who is involved in the psychedelic subculture. I believe there is mounting evidence that the young people who regularly use LSD and involve themselves in the psychedelic subculture develop a very profound alteration in psychosocial functioning.

What is the significance of this? Why do I belabor the point? I bring it up because many people seem to believe that young persons who are involving themselves with what can be called the psychedelic movement are going through a "phase" and will easily become "straight" again. The rationalization of those who hold this belief is that "these young people are just experimenting, as we did when we swallowed goldfish or went to fraternity games, and they will come back." It is my conjecture that at the very least the young people who are deeply and intensely involved in this movement will not easily be able to reenter the dominant American culture, because of a profound conflict in value systems. A person with the "psychedelic syndrome," committed to non-violence, will have great conflict in a society like ours where the ethic is violence and competition. I believe that the young people participating in the "hip" movement will not be able to reenter the dominant culture without having some very significant problems. So long as they remain in the psychedelic subculture their "psychedelic syndrome," with its characteristics of non-violence and magical beliefs, is actually respected. They cannot by the standards of that community be called mentally ill—only by the standards of our community. Therefore, so long as the individual remains in the psychedelic subculture, treatment of the "psychedelic syndrome" becomes as beneficial as treating some of our accepted religious institutions. Treatment is indicated and successful only if, for various reasons—monetary, parental, or whatever—the individual attempts to reenter the straight society. Reentry can cause severe psychological problems, and as a result "becoming straight" will be a much more difficult process than most adults predict.

On the other hand, the "acid head" community cannot live with the "speed freak" community because of the violent characteristics of the latter. As a result the "hippies" have left the Haight-Ashbury district, moving to the country where they can establish small rural communes which tolerate and reinforce their belief systems. Unfortunately, in the conflict of "speed freaks" against "acid heads," speed always drives out acid just as in the broader society the philosophy of violence always dominates the higher aspirations of non-violence, peace, and love.

DR. SCHMID: We have time for discussion and questions.

DR. WILLIAMS:* What proportion of people return to the straight society from the hippie society?

DR. SMITH: It must be emphasized that this movement is so recent that we do not have data to support an intelligent response to this question. In analyzing the population structure it is quite obvious that there exists a core or committed group and a large number of camp followers. ("Plastic hippies" is one term that has been used for the latter.) The majority of the younger people who move between the straight and hip society cannot themselves be called "hippies," in that they do not have an intense belief system. They are attracted to the music and certain of the statements that they have heard, but they are very unsuited to this life-style. This group, the teenage group, presents the major health and social problems in the community. It is impossible to state what proportions of such persons are converted and stay. With the introduction of speed as a dominant drug in the urban areas, it is progressively less and less. Unfortunately we are seeing a conversion not to a hippie life-style but a conversion to a compulsive drug-using life-style.

DR. EARLEY:† Are there any data available on the hard core, the inner core, so to speak, of the hippie community?

DR. SMITH: There is good evidence that the hippie subculture which contains hippies, sociopaths, militants, teenagers, plastic hippies, social scientists and newspaper reporters is still rapidly growing. I base this not so much on what we see in the Haight-Ashbury but on reports that I receive from across the country indicating that the total movement is increasing. I have received about fifteen consultation calls in the last six months about the hippie influx in other parts of the country. I have every reason to believe both from this information and from my personal observation in lecturing in other parts of the country that the hippie population is increasing.

Now, the direction of the movement is another problem. There is an initial phase of cooperation and sharing and philosophical idealism, and then the militants and thrill-seekers move in. That seems to be the natural history. To break up this pattern, the large communities in which these small subcultures develop must come to the conclusion that their own extremely negative reaction is the wrong approach. There is not a city yet that has said anything but, "You're not welcome. We won't give you anything." In other words, it appears that some city eventually will attempt to develop some specialized educational, medical, and social approaches in working with these alienated young people and, it is hoped, interrupt this negative trend.

QUESTION FROM AUDIENCE: What is the ethnic origin of the hippie culture?

DR. SMITH: We have every reason to believe that, at least in the initial stages, it is middle and upper-middle class Caucasian youths with the highest representation from the professional family background that mainly make up this group.

PHYSICIAN IN AUDIENCE: Would you comment on the therapeutic use of LSD in terminal cancer cases and in chronic alcoholics?

DR. SMITH: As you know, LSD has been suggested for these two disorders; and, as you also know, therapeutic research with LSD has virtually come to a halt in the United States. With regard to terminal cancer cases, there is virtually no work going on. There is a great deal of work on alcoholism going on in Canada, and we are receiving conflicting reports. Some of the initial reports were very optimistic, but a later report indicated that variables were not controlled. In other words, alcoholics who were given LSD were also given therapeutics of other types—community environment and increased attention — that produced an increase in the cure rate. When these variables were controlled, there was little difference between groups that were treated with LSD and those that were not. The recent studies have focused more on repeated long-term use of LSD, and I think the best work on this is going on in Czechoslovakia.

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†Laurence E. Earley, M.D., Associate Professor of Medicine.

Dr. Sokolow:* What are the factors which determine whether a curious teenager will become a permanent hippie?

Dr. Smith: Many factors come to mind. I think we are seeing the first wave of the mass-educated pill-taking society. It is interesting that teenagers have found many of the new hallucinogens by consulting the toxicity comments about drugs in the medical literature. For example, we had a small wave of Symmetrel® abuse because its toxic manifestations include depersonalization and hallucinosis. I receive inquiries about different botanicals from teenagers, and they are incredibly curious about drugs. I do not answer letters about botanicals, but it is interesting that in reviewing patients' histories this statement occurs over and over: "My parents used these drugs, alcohol, tobacco, caffeine, sleeping pills, wake up pills, tranquilizers." They learn that drugs can produce psychological states.

The disturbing feature is the failure of young people to question drug use under any circumstances. They do not question whether they should use a drug or not use it, but rather what drug should they use. For example, in our research into the hip community, we learned that 45 percent of the people interviewed have taken unknown drugs. This is a very interesting indictment of our drug-taking society. Most of these individuals will take a drug without the slightest idea of what it does. We saw this in San Jose where 4,000 pills of unknown nature were passed out among 16,000 teenagers at a rock festival and most of the pills were consumed.

We have created a drug-taking society, and the young people have extended some of our basic attitudes into a situation that is now completely out of control. Once they have become enamored of the properties of various types of drugs and begin believing in the esoteric properties, these young people become very vulnerable to a culture that has as its basis the use of chemical agents to create various psychological states. If one accepts the assumption that a pill will relieve anxiety, then it is not difficult to expect a drug to induce a religious experience or to increase learning. I believe we are seeing a continuum in which neither the dominant culture nor the hip culture questions whether drugs should be used. It is always more a question of what drugs should be used to achieve a particular psychological state.

Physician in audience: What relation does amphetamine use have to the alleviation of hostilities?

Dr. Smith: It is quite apparent that during adolescence all young people have hostilities. In going through the maturation process there are many complex problems, problems in sexuality and anger against parents. If individuals conclude that it is necessary to act out these hostilities and aggressions and that it is acceptable to take a drug in order to do so, then the whole country may act out in a violent manner. One of the reasons that marijuana is used is that it has sedative qualities and ability to relieve hostilities and antagonism. Young people become involved in the chronic use of LSD to handle their own internal aggressions and hostilities, but when they start using speed they externalize rather than internalize those aggressions. This is why I am concerned about speed. I am certainly not convinced that acting out an aggression does anything more than reinforce this attitude of hostility and aggression as a way to handling internal problems. People who take speed act out the natural hostilities and conflicts that one sees during the adolescent maturation process. It would be best if they could work them out without drugs. If they do select a drug (particularly speed) as a means for conflict-solving, the result may be destructive indeed.

Dr. Schmid: Thank you, Dr. Smith, for a presentation notable for both competence and compassion.

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HIBAC—Key Advisor to Medicare

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SINCE ITS INCEPTION, the Health Insurance Benefits Advisory Council (HIBAC) has served as a bridge of understanding and channel of communication between the health care community and the Medicare program. HIBAC does not make Medicare policy, but no regulation or major policy has gone into effect without thorough review and previous advice by this organization. In its continuing advisory function, HIBAC has assured the medical community an important voice and role in Medicare policy decisions and has helped mightily to cement relations between the government and the private sector.

As a measure of the care and thoroughness that HIBAC brings to its assignments, it should be noted that never has either of the two Secretaries of HEW under whom it has served disregarded or ruled contrary to any of the Council's recommendations.

Congress, in the Medicare law, provided for a Health Insurance Benefits Advisory Council which was established by then Secretary of Health, Education, and Welfare John W. Gardner in November 1965. Section 1867 of the law states that "for the purpose of advising the Secretary on matters of general policy in the administration of this title and in the formulation of regulations under this title, there is hereby created a Health Insurance Benefits Advisory Council which shall consist of 16 persons, not otherwise in the employ of the United States, appointed by the Secretary without regard to the civil service laws. . . . The members shall include persons who are outstanding in fields related to hospital, medical and other health activities, and at least one person who is representative of the general public." In capsule form, these two sentences give the nature and function of HIBAC.

Especially notable is the fact that this advisory council consists of private citizens and includes leaders in the health care field, as well as one or more representatives of the general public. Of equal note, in its advisory capacity, HIBAC does not establish the policies under which the program is administered; rather, it advises the Secretary of HEW with respect to the policies that are to be established.

The concept of establishing panels of private citizens to advise public officials on critical areas of administrative policy has long proven effective at every level of government. It was no surprise, then, that Congress would provide for such groups in enacting Medicare—a program that would affect the lives of millions of Americans and influence medical care in this country for years to come. Moreover, the Administration was in complete agreement with the Congress that the advisory role of HIBAC would be of vital importance to the implementation of the Medicare law.

I think that all of us who accepted appointment to the Council (HIBAC) in November 1965 appreciated the demanding task that lay ahead. Many of us, though, did not realize just how much time, effort, and energy would be required.

At its first meeting, 12 November 1965, the Council was called on to make recommendations on policy matters that would profoundly affect the delivery and reimbursement of health care services throughout the country. From the start, we were impressed by the fact that the Department of Health, Education, and Welfare wanted practical, down-to-earth advice — not platitudes or pious hopes — and needed it within the tight deadlines set up for launching the Medicare program.

Faced with this task, the Council met on 11 days in the first two and a half months after its establishment, and it has met nearly every month since. Many members, in preparing for the meetings, spent long hours in study or consultation with Government and health organization leaders. After

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Submitted 27 November 1968.

Reprint requests to: Mount Zion Hospital and Medical Center, 1600 Divisadero Street, San Francisco 94115.

presenting their views and findings at the meetings, the members decided — often (but not always) unanimously — on the recommendations that should be made to the Secretary concerning the policies to be adopted. These policies involved such complex subjects as conditions of participation and principles of reimbursement for hospitals, extended care facilities, home health agencies and independent laboratories, as well as reimbursement for physicians' services.

Unquestionably, this was a formidable task. However, my own confidence in the Council's ability to deal with this problem was enhanced by the qualifications of my fellow members. In appointing the Council, the Secretary provided for the broad representation of health care and other interests intended by Congress and, in addition, achieved a distribution of viewpoints, fields of competency and personal backgrounds that has assured full airing of all aspects of the policies considered by the Council.

The original Council members included:

Kermit Gordon, Chairman—Vice president of the Brookings Institution, an economist and a former director of the Bureau of the Budget. Mr. Gordon's term has expired.

William E. Beaumont, Jr.—Owner-administrator of Beaumont Nursing Homes of Little Rock, Arkansas, and past president of the American Nursing Home Association. Mr. Beaumont's term also has expired.

Bernard Bucove, M.D.—Health services administrator of New York City and former Director, Washington State Health Department; past president and former member of the Executive Committee of the Association of State and Territorial Health Officers.

Kenneth W. Clement, M.D.—Practicing surgeon, Cleveland, Ohio, and past president of the National Medical Association. Dr. Clement's term has expired.

Dorothy A. Cornelius, R.N.—Executive director of the Ohio State Nurses' Association and vice president of the American Nurses' Association. Miss Cornelius' term has expired.

Nelson H. Cruikshank—Former director, Department of Social Security, AFL-CIO, Washington, D.C., and past member of two advisory councils on social security.

C. Manton Eddy—Director of Aetna Insurance Company, Connecticut General Life Insurance Company and Connecticut General Insurance Corporation; past president of the Health Insurance Association of America.

Caldwell B. Esselstyn, M.D.—Associate program coordinator in the New York Metropolitan Regional Medical Program, the Associated Medical Schools of New York; former chairman and at present a member of the board of the Group Health Association of America.

Jose A. Garcia, M.D.—Practicing physician, Corpus Christi, Texas, and a member of the American Academy of General Practice. Dr. Garcia's term has expired.

The Very Reverend Monsignor Harrold A. Murray—Director, Department of Health Affairs of the United States Catholic Conference, Washington, D.C.; member of the President's National Advisory Commission on Health Facilities. Monsignor Murray's term has expired.

Russell A. Nelson, M.D.—President, The Johns Hopkins Hospital, Baltimore, Maryland, and past president of the American Hospital Association.

Howard P. Rome, M.D.—Senior consultant in psychiatry at the Mayo Clinic; councilor and past president of the American Psychiatric Association; professor of psychiatry, Mayo Graduate School of Medicine, University of Minnesota. Dr. Rome's term has expired.

Samuel R. Sherman, M.D.—Practicing surgeon, San Francisco, chairman of AMA Council on Legislative Activities and past president of California Medical Association.

Nathan J. Stark—Group vice president of operations of Hallmark Cards, and president of the Kansas City General Hospital and Medical Center Corporation.

Ray E. Trussell, M.D.—Director, School of Public Health and Administrative Medicine, Columbia University and former Commissioner of Hospitals for New York City.

Carroll L. Witten, M.D.—Immediate past president of the American Academy of General Practice and practicing physician, Louisville, Kentucky.

Ten new members have been appointed—seven to succeed those members whose terms have expird and three appointed in accordance with the Social Security Amendments of 1967 which increased the Council's complement from 16 to 19 members. The new appointees are:

Charles L. Schultze, chairman—Former director of the Bureau of the Budget, professor of economics at the University of Maryland and senior fellow with the Brookings Institution.

Margaret B. Dolan, R.N.—Professor and head of the Department of Public Health Nursing, University of North Carolina School of Public Health; member of the board of directors and past president of the American Nurses' Association.

Merrill D. Hines, M.D.—Medical director and chairman of the board of management, Ochsner Clinic; professor of clinical surgery, Tulane Medical School.

William R. Hutton—Executive director and director of information, National Council of Senior Citizens, Inc., and editor, *The Senior Citizen News.*

Syble H. Scott—Practicing attorney; nursing home operator; faculty member, School of Continuing Education, University of Oklahoma.

Herman M. Somers, Ph.D.—Professor of Politics and Public Affairs, Princeton University; past member of the Advisory Council on Social Security; consultant to many governmental and private agencies in the fields of administration and health services.

Adolfo Urrutia, M.D. — Practicing surgeon; chief of staff, Santa Rosa Medical Center, San Antonio, Texas.

Monsignor James Henry Fitzpatrick—Director, Division of Health and Hospitals, Catholic Charities, Brooklyn (N.Y.) diocese.

J. Minott Stickney, M.D. — Member of the faculty of the Mayo Foundation and the University of Minnesota.

Lionel F. Swan, M.D.—Practicing physician in Detroit, and immediate past president of the National Medical Association.

Throughout its first months of existence, the Council's agenda and priorities were dictated largely by the fact that the program had to be operational—with the exception of extended care services—by 1 July 1966. Consultation with the Council was required by law with respect to the conditions of participation for hospitals, home health agencies and extended care facilities. In addition, the Department sought the Council's advice on all other major policy areas before launching the program.

Before they were presented to the Council, of course, these matters were subjected to intensive study and consultation. The initial groundwork was laid by the staffs of the Social Security Administration, Public Health Service and Welfare Administration (now the Social and Rehabilitation Service) in consultation with experts in the health care community. Both the American Medical Association and the American Hospital Association established special committees to assist in this effort. Following these activities, work groups representing the viewpoint and experience of major professional and institutional interests were convened to review and refine the tentative policies that had been developed. These groups included persons suggested by medical, hospital and nursing home associations, insurance companies, Blue Cross and Blue Shield and public health organizations.

Typically, staff reports and pertinent background materials on each topic to be discussed are submitted to the members for study in advance of the meeting. Included is information on the legal framework within which policy must be adopted by the Secretary, the position taken by major interests and staff recommendations.

After preliminary staff discussions at the meeting, the Council begins the real hard core of its work. The members exchange opinions and reactions to the staff material, evaluating all aspects of the subject. If the members feel that they do not have an adequate basis for decision, they often request additional information from the appropriate Government agency or private organization. If they feel that there is sufficient basis for decision, but are sharply divided on what that decision should be, the members discuss possible alternatives that might prove satisfactory. Frequently, they request staff development of a number of such alternative proposals for presentation to the Council at a future meeting.

The time needed for the Council to reach a decision has varied widely. In some cases—for example, the conditions of participation for home health agencies—the members reached agreement on recommendations to be made to the Secretary after a single session. In other cases—for example, the principles of reimbursement for provider costs—many meetings, involving additional information and alternative approaches, were required before agreement could be reached.

There also has been wide variation in the nature of recommendations made by the Council. At times, a few critical issues of a policy could be isolated and recommendation geared to these issues. At other times, the Council has found it necessary to make its recommendations on a point-by-point, page-after-page basis. Examples of the latter include the conditions of participation for hospitals, extended care facilities and independent laboratories, and the principles of reimbursement for provider costs.

The extent to which such a diverse group could reach agreement on so many complex issues seems nothing short of remarkable. However, on closer analysis, several factors have helped to shape this end result. First, of course, the statute itself limits the area of controversy. We were not considering, for example, whether or not there should be a Medicare law or what the provisions of such a law should be, but how the law as enacted might best be administered.

Secondly, we decided early to seek unanimity to the fullest extent possible after resolving different viewpoints. We felt that such an approach would be more useful to the Secretary than recommendations imposed by a majority, with a substantial minority in dissent (although this has occurred on occasion). In addition, this approach often forces the Council to find new and fresh solutions that often prove more acceptable to members than the positions they originally advocated.

Third, and I believe most important, the Council agrees on basic goals. While the members represent diverse viewpoints, they share the common goal of recommending program policies that are workable, fair and consistent with our mutual objective of high quality care.

The Social Security Amendments of 1967 contained several provisions which affected not only the size but also the functions of HIBAC. Among the most important were the previously mentioned increase in the number of members from 16 to 19, and transfer to HIBAC of all functions of the National Medical Review Committee (NMRC), which had not been appointed. Thus, in addition to its other responsibilities under Title XVIII, the Council has assumed the NMRC mandate "to study the utilization of hospital and other medical care and services for which payment may be made under this title with a view to recommending any changes which may seem desirable in the way in which such care and services are utilized or in the administration of the programs established by this title, or in the provisions of this title." In addition, the 1967 amendments require HIBAC to submit an annual report on the performance of its functions to the Secretary of HEW for transmittal to Congress, and to engage such technical assistance as required to carry out its functions.

To meet its new responsibilities the Council established an Ad Hoc Committee on the Evaluation of the Delivery and Use of Services under the chairmanship of Dr. Ray E. Trussell. In addition, to support the Commitee, the Council created task forces in the following areas: research and statistics; hospital and extended care services; home health services; medical services; and laboratory services. During the past several months each task force has been reinforced by ad hoc consultants appointed for service as necessary because of their individual competence, and/or because they would bring to HIBAC the views of important groups and organizations. Included among the consultants have been representatives of organized medicine, providers, the insurance field, and consumer organizations. This approach emulates the tremendous original efforts of the Social Security Administration to obtain maximum consultation in implementing Medicare. In this way, outside involvement will continue in the review, reporting and recommending process.

I hope that I have fully conveyed the fact that the Health Insurance Benefits Advisory Council is a vital, dynamic and ongoing group—one which has successfully helped to bridge the gap between the private and governmental sectors and one which has had an important voice in every Medicare policy.

In commending the Council for its contributions, HEW Secretary Wilbur Cohen said: "The successful launching of the Medicare program and its solid accomplishments . . . are due, in large measure, to the able and perceptive services of the Council's members. . . . I am grateful that we have had the benefit of their wisdom and special skills in this important undertaking. They have earned the gratitude of the Federal Government and of the millions of beneficiaries of the Medicare program."

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California Medicine

EDITORIAL

Student Unrest

An Editorial Symposium

The following editorial was sent to a number of senior medical students who had been nominated by their deans for participation in discussions with the Committee on the Role of Medicine in Society. They were asked to comment on the editorial and to express any other thoughts they might have on the subject. The four replies received are included in this unique "editorial symposium."

STUDENT UNREST IS a fact of life in today's world. It is easy but quite untrue to assume that it is all a product of Communist intrigue, or the work of leftist professors in schools or colleges, or simply a modern manifestation of the age old phenomenon of adolescence trying to find its identity and the limits of its strength. The evidence is that the student unrest of today is something much deeper, more profound, and with far greater implications for the good or ill of society. Today's student unrest has now crossed the threshold of our medical schools and it behooves us to understand it if we can.

It is quite difficult for the generation which makes up what is called "the Establishment" to understand what it is like to have no memory of the Great Depression, World War II or even the war in Korea, and to have lived only during a period of unbelievable technologic progress and ever increasing economic prosperity. Much of this generation of students has known only comfort and even affluence, or if not, the lack has been made specifically clear to them through television and other means of mass communication which incessantly give the hard sell to luxury items and luxurious living. The students of today who are of the "haves" are deeply sympathetic with the "have nots" whether these be students or not, and they seem to accept more literally than their elders the proposition enunciated in the Declaration of Independence for all to hear "that all Men are created equal, that they are endowed by their Creator with certain Unalienable Rights, that among these rights are Life, Liberty and the Pursuit of Happiness." An equal opportunity to health is considered to be among these rights, but it goes much further than this. The "have nots" are determined to become "haves," and the student generation by and large believes that this is just and that fulfillment is not only possible but in their opinion long overdue. It is important to remember that they have repeatedly heard it said by the highest authorities in the land that this nation has the resources and the technologic capability to attain many of these humanitarian goals if it only chooses to do so. Perhaps for these reasons, perhaps for others, many in the student generation now appear convinced that the "Establishment," either through ineptness or intent, is in reality obstructing progress by giving only lip service to its ideals while in fact exercising oppression or repression of one kind or another to maintain the unsatisfactory status quo. The apparent disparity between what the "Establishment" seems to *say* and what it seems to *do* strikes many thinking students as little short of indefensible hypocrisy.

It is somewhat more difficult to identify and assess what it is that energizes the student unrest. To be sure, the time span over which youth achieves an adult identity has become unnaturally prolonged. Biological maturity comes relatively early and the right to drive, the right to kill, the right to vote and many other prerogatives of adulthood come along before any real responsibility for themselves, their mates, their children or for society. The time lag between the acquisition of adult rights and the assumption of adult responsibilities results in a kind of prolonged social adolescence for many in the student generation, with all that this implies for the use or misuse of their growing social, economic and political power.

The Protestant ethic has always been strong in this nation, and there are many who believe that guilt is an important energizing force underlying much of today's behavior. It is interesting to speculate upon how much this may contribute to student unrest. There is an undeniable sense of national guilt with respect to the plight of the blacks and the exploitation of certain other minority groups. This is shared by students, some of whom also feel that they personally have had it much too good and find themselves uncomfortable trying to live in comparative luxury with their own humanitarian ideals. And among the blacks one can sense a feeling of guilt that too few of them have been able to shuck the psychological shackles of the slave culture and make their mark as free men in a free country during the century which has passed since slavery was actually abolished. Where guilt feelings such as these exist, they rankle and are easily projected to parents, the older generation or, better yet, to the Establishment, who are held to be guilty of not having lived up to their expressed ideals, else the inequities which are to be seen everywhere would not exist. There is substantial evidence that much of the student generation—rightly or wrongly, and whether black or white—does in fact project the guilt and the blame upon the Establishment for permitting these "injustices" to occur and to continue.

The Establishment is also held responsible for Vietnam, which is viewed by a large number of students as a cruel and unnecessary war being fought by conscripts from their own age group for lofty stated purposes which seem utterly incompatible with the methods used to fight this war, which to them are far from lofty and too often brutal. For many, their opposition to this war and the draft seems linked with a need to prove their own personal courage both to themselves and to their peers in some sort of confrontation or trial by fire. One can but speculate upon how much this contributes to the student unrest which is so evident.

Whatever the reason, many of the student generation seem anxious or even compelled to identify with those whom they consider to be the victims of real or imagined "oppression," which they rightly or wrongly attribute to the Establishment or one or more of its many institutions. This identification may be with those students who consider themselves oppressed by archaic college rules or the caprices of a modern college computer. It may be with blacks seeking to overcome educational disadvantages, with teaching assistants who believe they are unfairly exploited by their academic superiors, with migrant workers in need of health care, or the victims of poverty in the ghettos. They may be joined in their identification by members of the academic Establishment whose individual or collective moral conscience may become aroused. Whatever their motivation, these identifications are real and often very deep and filled with meaning to the student.

The student unrest of today reflects the fact that these young people are largely action-oriented. They are impatient to achieve the goals of human equality and the right of life, liberty and the pursuit of happiness. They seem to feel a need to prove themselves. The Establishment has become the target of this unrest, since in the view of these action-oriented students it has fallen far short of accomplishing what it should. They know that the Establishment is there, that it is in power, and that they must somehow deal with it and its various institutional components. The action may be to withdraw, and some of their generation have eschewed the Establishment and all its works to seek equality and self-fulfillment in non-conformist and often drug-assisted ways. This is a certain empathy among students with those who have tried this, but most seem to recognize this approach to be quite vacuous. The activist road, as the action-minded student would view it, is to force changes in the Establishment by making demands upon its institutions and by banding together with any allies they can muster to bring sufficient pressure to bear to force acquiescence to their demands. This has proven to be an unexpectedly effective technique. It has already produced substantial changes in the status quo in many schools, colleges and even medical schools.

This student power is now becoming substantial. When responsibly exercised it has proven to be constructive and capable of producing needed and often long overdue change. But as with any substantial power, if irresponsibly used or perverted it can be devastatingly destructive. When this occurs it is often because relatively unstructured student empathy and equally unstructured faculty sympathy become captured and then perverted by those who secretly or openly avow that they would destroy the whole Establishment, or as many of its institutions as possible, on the grounds that they are so rigid in their thinking and entrenched in their power that they can never be made into effective instruments of progress and like dead limbs on a tree, they should be cut off and destroyed. It is a very small minority of students that has advocated this nihilistic approach to progress, but at times — often with leadership and support from off the campus — they have been able to create situations which for practical purposes have accomplished their destructive aims.

No matter what, the restless and action-oriented student generation of today will soon become the Establishment. It may safely be predicted that the unrest we see now among students will before long become the unrest of the Establishment. The student generation is idealistic, it is numerous, and it is tasting of social, economic and political power at a much earlier age than did its forebears. These are times of change. The rate at which the change will occur is most important. It is certain to be more rapid than would have been thought possible a short time ago. It is crucial that the rate of change be controlled by the exercise of reason and the restraint of emotion, and that change be kept evolutionary and constructive rather than revolutionary and therefore tragically destructive to a complex technological society. Fortunately there is much responsible student leadership which can be aided, abetted and strengthened, and fortunately the vast majority of the student generation really want education, responsible progress, and not destruction.

In our profession organized medicine is held suspect by many medical students. It is considered by them to be part, perhaps even a bulwark of the Establishment, seeking to preserve the status quo at all costs. The need for better two way communication and fuller understanding between students of medicine and the practicing profession is obvious. There must be open minds, steady hands, firmness and flexibility all the way around, and there must be more clearly visible progress toward the common aim — a closer realization of the goals of human equality and the right to an equal opportunity for health. It behooves organized medicine to understand the idealism which underlies student unrest in universities and particularly among medical students, and to join with responsible student leadership and help to achieve their goals, which are fundamentally the same as the goals of medicine's Establishment—"The betterment of the public health" and the betterment of mankind.

To the Editor: I am a naive critic, not fully understanding the editorial temperance which attempts to find the ground between saying nothing and saying too much—overwhelming the reader with threatening and therefore rejected ideas. However, I feel that the article has overplayed student unrest as a psychosocial phenomenon. Though I agree with much of the speculation about these factors I don't feel it contributes significantly to dialogue with disaffected students. Psychosocial factors are more of a curiosity to those seeking an easy rationalization, than to those trying to tune in on what students are saying. In trying too hard to understand the medium, one risks missing the message. As a semantic twist, an editorial might explore the social conditions and national policy which *unrest* conscientious students and others. Among the more troublesome of these are the *white problem* with its variations on racism and oppression, poverty and starvation, the conflict between authoritarian institutions and the quest for participation, and an unjust, decimating and cruelly maiming war. Of peculiar concern to medical students are the irrelevancy of the forms and curriculum in their education and the inequitable distribution of health care. In a time when heart transplants are considered a therapeutic alternative, many do not have access to the advances of decades past. In addition, many students and physicians find subjugation to the military intolerable to their humanitarian practice of medicine—only to mention the absurdity of participating in a dehumanizing process which measures success in numbers of killed or wounded.

I take issue with the discussion of revolutionary vs. evolutionary change, though it may be largely a semantic issue depending on how one views the magnitude of the problems. We cannot wait for evolution, already decades behind, to catch up with the starving, impoverished, sick and oppressed, or to stop the mockery of human life which is the Vietnam War. Too much has already been tragically sacrificed to "our complex technological society." The problems require revolutionary change directed by the same reason and compassion which initiates it. This is not to say that such change will not be unreasonable to those entrenched in the ways and thinking of the Establishment. The word "responsible" is often connected with dissent. A dissenter's "responsibility" varies with the degree of his conformity to the Establishment, not with the justness of his cause. Hence the paradox: irresponsible, unreasonable revolutionary change may also be just, meaningful, constructive progress.

These are fragmentary thoughts on a well conceived editorial. My bias as an unrested student is the hope that others will also become unrested—it is also the intemperance which makes candid student opinion a less useful tool in bending the minds of your readers than the proposed editorial. Possibly a symposium of unrested student opinion could appear in some succeeding issue.

RANDALL T. HERMANN
Fourth Year Student
University of California, Los Angeles

To the Editor: I appreciate your consideration in forwarding the proposed editorial for the February issue of CALIFORNIA MEDICINE, "Student Unrest," to myself and the other students involved in the meeting of the Committee on the Role of Medicine in Society for our frank evaluation.

It is a fact that a certain percentage of the student population in medical schools today is deeply concerned with and involved in the problems of our society in general, and of the role of medicine in that society specifically. It is apparent to me, however, that this percentage is still rather small, due in large part to an emphasis in medical education today which is anything but conducive to involvement in society. I am also aware that there are those in the medical "Establishment" who are vitally concerned with meeting the challenges presented to organized medicine by a rapidly changing society. Unfortunately, their numbers are also few. One of the obstacles to actively involving larger numbers of both students and physicians has been a lack of communication. The initiative of the CMA in formally recognizing the student voice is at least a step toward improving diplomatic relations, and is a trend which I hope continues.

As far as the editorial is concerned, I have a mixed reaction. Perhaps this is because the article is somewhat confusing, or rather ambiguous. My feeling is that it strives too hard to please everyone. It has been my understanding that "editorial" implies an opinion, a definite *stand* on an issue, not an unbiased report of the events by a non-participant. You are obviously not a non-participant, but I feel that you have avoided the real issues. After beginning the editorial by establishing the fact that student unrest is real, you then state, "it is somewhat more difficult to identify and assess what it is that energizes the student unrest." My feeling is that an article dealing with the "what" of student unrest, with the specific issues, rather than one attempting, in the popular mode, to psychoanalyze the movement, would have been more appropriate. I think that you will agree that it is a *fact* that organized medicine does not at the present time have an adequate system of health care delivery. I hope that you will also agree that it is a goal of both the students and the Establishment to correct this situation. The *issue* is how this may be accomplished best, and an editorial dealing with this question might be instrumental in promoting progress.

As the editorial stands now, my interpretation is that you have said essentially the following: "Fellow Establishmentarians. We had better wake up and realize that 'student unrest' is a reality. As energized as they may be by subconscious guilt feelings which are unjustifiably projected to the innocent Establishment, and by a 'prolonged social adolescence' which they cannot help, they are none-the-less attracting considerable attention. If we are to preserve our traditions, we had better soothe and harness these forces soon, and ensure that evolution, rather than rapid change, continues to be the order of the day." I feel, as do many students, that we are already far enough behind the eight-ball. Evolution (sometimes known as "procrastination" or "paying lip service") has in this instance proven itself to be inadequate. Revolutions are happening not infrequently today, especially in technology. They occur, and they are not necessarily destructive, as you seem to imply. Sociologically, we need to catch up, and organized medicine has more catching up to do than most present-day bureaucracies. If we, as physicians, do not do this ourselves, it may be done for us.

In summary, then, I feel that it is a watse of time for the CMA to publish articles about "student unrest," and for students to issue editorials on "the Establishment." Let us stop suspiciously examining each other, cautiously feeling each other out. If, indeed, we have the same goals, then let's join forces and write editorials about these specific goals and how to achieve them.

Thank you again for the opportunity to express my opinion.

STEPHEN P. BOYERS
Fourth Year Student
University of California, Irvine

To the Editor: In responding to this editorial I should first state the position from which I speak. Though I usually support the activists, I am on friendly terms with the "Establishment." I hope to serve both now as an interpreter. Since I am speaking to the Establishment I shall not be neutral, but advocate the activist position.

Numerous fundamental assumptions separate the generation in power from the radical-and-student alliance. I am only aware of a few of these differences in worldview, but I will try to give you a brief sketch of some of the points of schism as I see them.

One of the basic differences is that the older "haves" believe much of what those in power say. They view America as basically a benevolent, peace-loving country, dedicated to the enrichment of the lives of all men. They believe those in power when they say that we abhor violence, domestic and foreign, and that we support the right of every man to lead a happy and productive life free of unreasonable restraint on his personal freedom, under a government of his own choosing.

Students generally, and radicals endorse these goals, but doubt the veracity of those in power who profess them. They test the assertions against the reality of history. They point to our support of repressive and oppressive regimes throughout the world, and ask how we can do this if we have the best interests of the people in those countries at heart. They point to the billions of dollars American business has invested in these "stable" regimes. They note that we buy raw materials very cheaply and sell manufactured goods at handsome profits in these "free" nations. It is generally agreed among young activists that our foreign policy serves American business interests, principally, and that our penetration of world markets is a exploitative as those in power dare make it. To maintain this system most radicals believe that we establish and support governments under which most Americans would rise up and rebel.

Our power structure says it wants black people to be freed of their economic and social restraints, and yet repressive measures like 1964's Proposition 14 draw support from major segments of the power structure. We abandon vital economic and social reforms in order to spend the money killing human beings in Vietnam.

In contrast to the commonly held belief that we are a non-violent, peace-loving nation, most student activists see us as a nation conceived in and permeated by violence. They cite our genocidal slaughter of American Indians, and our invasions of Mexico, Cuba, Panama, Puerto Rico, Haiti, the Dominican Republic, the Philippines, Nicaragua, and other hapless states. Our habit of shooting and lynching people is still a scandal in Europe. Lastly, they note that the Establishment only condemns non-government violence. The public is made acutely aware of property damage at San Francisco State College, but there is no condemnation of the police when a student is Maced, arrested, and held without medical attention while corneal ulcers form and ultimately penetrate the stroma. They feel that the President's commission on the causes of violence is hypocritical if it does not consider the violence we perpetrate in Vietnam. In Chicago this summer students showed unequivocally that the government will resort to the most violent repression. Younger people, who wanted our unconstitutional war voted on, learned that this is really a limited democracy with strong totalitarian potential.

In the editorial the question of why protests so often become violent was raised. Part of the answer lies in the fact that leaders of the radical movement have found that they can very quickly "radicalize" previously uncommitted people by arranging to have the police bludgeon them or other bystanders. Once kicked and clubbed, the new radical is much more inclined to take direct action. In fact, this is what separates him from the previous generation of dissidents, the "liberals." That term is now a dirty word in radical circles, where it evokes the image of an endlessly debating feckless intellectual, who sees all sides so clearly that he supports none. Young radicals feel that thought uncoupled to action is self-indulgent and hypocritical.

It is reasonable for students to be restive if they believe, and they do, that their country is doing wrong and refusing to recognize it. To be docile under such circumstances would be cowardly and unpatriotic. Student activists feel that every day we pursue our present national course means death, disease, and poverty for countless people both here and around the world who have the same inherent worth and the same fundamental right as we to enjoy the world's largesse. When a major avenue of change, such as the party primaries, is closed, as happened in Chicago, the level of desperation rises, alienation increases, and the temptation to break the law grows.

Activists among medical students are much more attracted by the Medical Committee for Human Rights than the AMA. They feel the AMA was at its best at the time of the Flexner Report. At that time it was willing to see reality for what it was. Now, they feel it has degenerated into a rear guard action against the reforms of the New Deal. They feel the AMA is now principally concerned with protecting the economic interests and prejudices of its members, not assuring the best possible medical care for those who need it. The often repeated assertion that we have the best medical care in the world does not appear to be true. In a country which has our potential and our public health record such an assertion is a cruel joke. If today's medical student activists join organized medicine, it will be only to get the necessary hospital affiliations. Most of them expect to earn a living commensurate with their education and effort, but they're not wed to fee-for-service. Socialization is generally considered inevitable, and after a period of adjustment, probably better for more people. Most activist medical students feel that organized medicine should be working to avoid the terrible mistakes made in England and elsewhere, not just opposing the whole idea. They hold that health care is a right, not a privilege, and the fundamental mechanisms for meeting medical needs must be re-examined.

In the conflict which is inevitable as our ideas and world-views collide both sides will be enriched if we can base our discussion on verifiable facts, if we can take each others' ideas and experience seriously, and if we look at the position of responsible spokesmen on each side, not the isolated acts of the few.

Brian D. Johnston
Fourth Year Student
University of California, San Francisco

To the Editor: First, I'd like to say that overall I am delighted with the content of the editorial; it understandably pleases me that your view is fundamentally sympathetic toward the substance of student unrest and pleads for a broad understanding of its roots. I of course concur with the denial that student dissatisfaction is sparked by any particular doctrinaire ideology. It has been accepted for quite some years that young children have capacities for perception of social and interpersonal disturbance and pathology which are usually bred out or suppressed during the process of "maturation"; I would extend this acuteness of children, at least partly, to the students who now are "creating" such turmoil on campuses and in medical schools. After all, dependent children have much in common, as regards denial of self-determination by parents, with the student generation whose dependence is prolonged. And isn't the most common argument against active student participation in design of their own curricula and in determination of certain policies of educational institutions, just that argument which supports prolonged dependency—namely, "you haven't the experience or perspective to make reasonable choices."

I think it will be of great importance to understand both the common and disparate roots of student unrest as manifested in every Western and some Eastern countries; there is no doubt that there has developed a set of formally-unrelated student protest movements around the world. Little has been written to date which sheds light on this apparent coincidence, for it certainly is not the result of organized international effort. Indeed, the whole Western World, with a few exceptions, is experiencing unprecedented affluence. It seems that it is just this fact which can explain part of student agitation: the affluence is not uniform; and full bellies and a roof have generally been considered prerequisites to the development of concern about the quality of life, which is so much a motive force in student revolt. O.K. It seems that I am really just saying I agree largely with what you have written. Perhaps I can add a little to that.

Whatever the sources and aims of student unrest, I believe that at least in this country it bears a fair share of the American trend toward anti-intellectualism which we see in electoral political life, proposed "solutions to crime in the streets" (some of which "solutions" smack of Final Ones), and the widespread arming of individuals to protect their "rights and property." I would have hoped that the student generation might, in its protest, have provided an effective counterforce against growing anti-intellectualism; I see little of applied intellect or respect for rational processes operating among dissatisfied students now, be they organized into groups like the Black Students Union or the Students for a Democratic Society, the Student Health Organization, or the reactionary campus groups for "campus order," or be they simply depressed, apathetic, uninvolved, and personally alienated individuals. Activism need not shun rationalism, but too often the two habits of mind are viewed by students as irreconcilable. What of the older generation and those of them who ally themselves with the "Establishment"? Two factions have emerged, just as among the students: those who blindly support the students, either because of personal fear of aging and exclusion from where it's at or because of the opportunistic belief that they can capitalize for their own gain on the disruption that students are capable of producing; and those who blindly condemn the hippies, yippies, activists, blacks, and youth in general, those who would line the young whites and blacks up against the wall and shoot to kill. Of course there are shades between these two extremes, but they (I count you among them) are rarely heard in public.

I see not only around the country but on my own medical school campus a wholesale rejection of previously honored human and intellectual values which might temper the polarization of attitudes and actions which increasingly threaten and carry out the destruction not only of gentleness and clear thinking, but also of life. If the students out of frustration and a sense of their burgeoning power have discarded humanism in their actions, their elders must *not* do so. If the students are willing to injure those whom they consider the agents of murder in Vietnam, on the streets of every American city, and in the hearts of every ghetto, this gives no right to reaction and displays of traditional power to the generation of their parents. *They* are the ones, by their own arguments, who supposedly have the "experience and judgment" to reverse some of the destruction. Their credibility is rapidly disappearing. I do not mean to renounce responsibility either for the good and hopeful grounds of student revolt or for its destructive and hateful aspects; I as a student bear both burdens and have no clear solutions. And I'm afraid I'm pessimistic about the value of exhortations.

I wish I could have contributed more. But I'm awfully glad you wrote as you did.

SOO BORSON WRIGHT
Fourth Year Student
Stanford University

The Early Detection of Diabetes

IN THE PAST the most significant advances in patient care have resulted from the prevention of disease rather than from the treatment of its complications. The future of medicine seems to lie in the same direction. For example, despite the growth of knowledge about antibiotics and microbial metabolism, infectious diseases are still better prevented than treated. Even the dramatic surgical approaches to cardiovascular diseases must be considered temporizing measures until the biophysical and biochemical nature of pathologic changes in vascular tissue is understood better. The value of the prevention as against the treatment of disease is indicated, in the chronic diseases, by the fact that the elucidation of the biochemical abnormalities and specific enzyme defects in such inborn errors of metabolism as galactosemia, fructose intolerance, cystinuria, and phenylketonuria has made it possible to prevent the development of cataracts, cirrhosis, mental retardation, renal tubular disorders and recurrent renal stones. Careful study of inherited diseases has shown that early detection and therapy can prevent the development of permanent morphological and perhaps biochemical changes. Although there are unresolved problems, the successful management of many of these diseases depends primarily on early detection in the affected individual.

As we expand our understanding of the biochemistry of disease and the mechanisms of drug action, the principles of the treatment of inborn metabolic diseases will be extended to the common chronic diseases. Clinical practice will deal less with the treatment of the established complications of disease and more with the early detection of the predisposed, asymptomatic patient. We have not yet reached this stage of medical practice, but there is evidence that we are entering this era in the treatment of some chronic illnesses.

Diabetes mellitus is not one of the diseases for which the biochemical abnormalities are defined clearly. Nevertheless, the detection of patients with asymptomatic diabetes—pre-diabetes, latent chemical diabetes, and chemical diabetes[1]—is of more than academic interest. Stowers[2] has shown that sulfonylurea treatment of chemical diabetes may lead to a remission of the laboratory abnormalities of diabetes. Glucose tolerance tests in a large number of the patients with chemical diabetes remained normal three weeks after chlorpropamide therapy was stopped. In contrast, chlorpropamide did not produce a remission of diabetes in any patient treated after the disease had become symptomatic. Further, in some patients with reactive hypoglycemia and either latent chemical diabetes or chemical diabetes, a short course of chlorpropamide therapy led to a remission of symptoms and a normalization of the plasma insulin response to oral glucose.[3] Improvement was maintained for at least one year after chlorpropamide was discontinued (longest follow-up available). These observations suggest that the sulfonylureas may correct the basic abnormality in the diabetic person when the disease is treated in its early stages. Also, it seems from the data of Stowers[2] that at some time in their course the changes which produce diabetes become irreversible.

It is still too soon to know whether early sulfonylurea therapy will lead to permanent remission of diabetes in some patients, or whether long-term therapy of a person with asymptomatic diabetes will decrease the incidence of vascular complications. More work is required before these questions can be answered. However, the data cited above is the most encouraging we have had with respect to the prevention of the long-term complications of diabetes and stress the importance of the early recognition of this disease.

This last point is emphasized by Alexander in an article published elsewhere in this issue of CALIFORNIA MEDICINE, reviewing the problems associated with the early laboratory diagnosis of diabetes. Alexander has reviewed the relative merits of the various tests used to measure glucose metabolism and has indicated the usefulness of the determination of plasma insulin concentrations. An important point which has been emphasized is that although the diagnosis of diabetes is based largely upon finding an abnormality of glucose metabolism, this is not specific for diabetes. The possible presence of other endocrine diseases, drug ingestion and the nutritional status of the patient must be considered in planning and interpreting the results of glucose tolerance tests. Alexander has pointed out that the diagnosis of diabetes is not made when it should be or is made without adequate laboratory evidence in a surprisingly large number of patients.[4]

Thus, it is essential that we pay closer attention to the diagnosis of diabetes, especially early in its course, if the advances of medical research are to have full impact on improving patient care. It is important also to consider that an improper diagnosis of diabetes will be as harmful as failing to make the diagnosis when it is warranted, not only because of the effect on the patient, but also because false positives will lead to erroneous interpretations of studies designed to measure the effectiveness of early treatment.

We are entering a new era in the treatment of diabetes. As with many other diseases, optimum management of this disease will depend on early detection of the predisposed and asymptomatic patients.

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Treatment of Incurable Endocrine-Sensitive Cancer

THE NOW WELL documented fact that patients with certain cancers, even with widely disseminated metastatic disease, may enjoy improvement in the quality and length of their lives as the result of various treatments is emphasized in a timely review in the January and February issues of CALIFORNIA MEDICINE.[1] This thesis deserves the attention of all practicing physicians in these days of increased longevity and ever increasing numbers of patients with cancer, many not detectable at a stage when they can be cured by surgical or x-ray therapy. Evaluation of the voluminous literature on this subject is extremely difficult because of different methods of selection of patients for therapeutic trials and very great differences in endpoints taken as indications of successful therapy. The author attempts to grapple with these frustrating problems and to bring some rationale into the presently chaotic body of conflicting data. In so doing he has been properly cautious, restricting his conclusions to facts observable from clinical experience such as responsiveness of tumors to hormonal therapy rather than the clinically less provable concept of hormone dependency. For example, it is difficult to explain why the same breast cancer which responded to oophorectomy subsequently responds to estrogen treatment. Unhappily, no one knows what causes cancer, except in rare situations such as the scrotal cancers of chimney sweeps described by Percival Pott two centuries ago. Eventually, however, clinicians will have to face the problem of cancers arising in women given contraceptive mixtures containing estrogens. These, of course, are actuarial considerations requiring accurate knowledge not only of incidence, but also numbers of women at risk and the length of exposure. Present data are, for the most part, reassuring despite occasional anecdotes of "a case."

It is salutary that surgeons recognize that nearly half their patients subjected to radical mastectomy will go on to dissemination and that prophylactic castration has not yet proved its worth. Nonetheless, disseminated cancer of the female breast is often surprisingly consonant with considerable longevity, apparent good health and productive life. The period of longevity and productivity is lengthened in those patients whose disease responds to appropriate hormonal palliation. Furthermore, many of the disabling symptoms of cancers are now known to result from metabolic or hormonal principles produced by the tumor, the effect of which can be recognized and corrected. Perhaps the most cogent example is hypercalcemia, which can almost always be corrected even if the underlying disease is refractory to treatment. Actually, this particular metabolic complication usually responds to simple measures such as hydration and short-term corticoid therapy. There is little excuse now for therapeutic nihilism by the physician in the belief that treatment of disseminated mammary carcinomatosis "merely prolongs the agony." In pre-menopausal women whose disease is beyond surgical or roentgen therapy, castration is established as the most effective treatment. The surgeon then often prefers further endocrine ablative procedures, especially adrenalectomy, rather than the use of pharmacological therapy. Dr. Crowley quotes the important work of Elwood Jensen, but has not included his perceptive limerick[2]:

> "A lady with growth neoplastic
> Thought castration just a bit drastic.
> She would fain [treat]* her ill
> By taking a pill —
> Which isn't completely fantastic."

Actually, Jensen's thesis well supports the author's logical belief in sequential therapy. Most physicians prefer to use the most innocuous and effective treatment first, and to save more drastic approaches — chemotherapy and endocrine ablative operation — for a later period. For this reason, we would suggest deferring ablative treatment, in part because it makes subsequent chemotherapy much less well tolerated. But treatment must be individualized; for example, the patient with a rapidly growing tumor may require appropriate chemotherapy first rather than last. The review points out that oophorectomy of the pre-menopausal woman before its effect upon breast cancer can be evaluated destroys the best indicator for subsequent adrenalectomy or hypophysectomy. In patients whose disease does not objectively respond to castration, neither subsequent procedure yields sufficiently high regression rates to justify such drastic surgery. No other piece of information so well selects those patients who will respond to ablative procedures despite a plethora of confusing and conflicting data on chemical discriminatory tests. And even when patients are carefully selected, overall results are *not* better than those of administrative hormonal therapy.

The studies of the Cooperative Breast Cancer Group have generated firm figures on responsiveness of patients with various variables (age, sites of dissemination, previous treatment) so that appropriate therapy may now be tailored to the individual case. Clearly, our present treatment is far from optimal, and much more carefully controlled clinical research is needed. It is noteworthy that several compounds have been reported to be as effective as testosterone but with far less capacity for the distressing virilization this compound produces. The Cooperative Breast Cancer Study Group has recently confirmed the observations that the antitumor effect of corticoids can be increased by the addition of triiodothyronine (50 micrograms daily) and the undesirable hormonal effects ("side-effects") of corticoids entirely avoided by the use of innocuous doses (for example, cortisol 30 mg daily). Since patients who have had hypophysectomy necessarily receive this treatment as replacement therapy, it is even possible that the good responses attributed to hypophysectomy may actually be the result of the hormonal replacement.

The review happily includes comments on the inadequately publicized report of the deleterious effects of prophylactic stilbestrol in men with prostatic carcinoma in an extensive Veterans Administration Hospital study. Despite a reduction in deaths from cancer, there was a greater augmentation of deaths from cardiovascular disease in estrogen-treated men. In view of some current hypotheses on the effects of estrogens on serum lipids and atherosclerosis, this observation should have a sobering effect.

Experience with the use of progestational agents in the treatment of endometrial carcinoma has now been evaluated sufficiently to indicate its value. There is also now sufficient evidence to indicate the desirability of giving maximal tolerated doses of thyroid hormone to patients with most thyroid cancers. In contrast to cancers arising in these endocrine-sensitive organs, it is now well documented that certain other tumors, notably cancers of the kidney and certain kinds of leukemia, also respond to endocrine manipulation.

Clearly, the therapeutic approach to the patient with disseminated cancer is undergoing considerable improvement by this type of study. It is now established that roentgen therapy, well chosen administrative and ablative endocrine manipulation, and chemotherapy of the patient with responsive disseminated malignant disease not only adds years to life, but much more important, life to years. Establishing this single fact has required the work of some of our best scientific minds, great cost, and enormous effort. We, as clinicians, must see to the application of this information for the benefit of our patients.

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*"Cure" in the original, unfortunately, not yet justified.

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Guest Editorial

Erythroblastosis Fetalis—Now a Preventable Disease

A WELL-KNOWN PROVERB states that "an ounce of prevention is worth a pound of cure." Modern medicine multiplies this differential not merely 16 times but usually many hundred- or thousand-fold. With continued medical progress, more and more conditions are responding to the preventive use of micrograms of material administered in a few minutes when, formerly, days of effort and kilograms of drugs—not to mention untold hours of anxiety—were expended in treatment of serious disease. A recent example of this kind of progress is the prevention of erythroblastosis fetalis, more properly described by the term "hemolytic disease of the fetus and newborn" due to maternal Rh antibody.

This past year, there became available commercially* a gamma globulin concentrate of anti-Rh serum. This material, called RhoGAM®, will block or prevent the immunization or sensitization of an Rh-negative woman recently delivered of an Rh-positive infant. Previously, each such pregnancy represented a risk of 1 percent to 10 percent, or more, of inducing Rh antibody production. This, in a subsequent Rh-positive pregnancy, could produce hemolytic disease of the fetus and newborn in varying degree — from the severest form (ending in death of the infant *in utero*) to the less acute type (showing anemia at birth) and mild varieties (having compensated anemia and jaundice, but treatable after birth). With four million pregnancies in the United States in 1960, it is estimated that erythroblastosis fetalis accounted for about 10,000 stillbirths and 40,000 live-born affected infants. Of this latter group, some 36,000 to 38,000 recovered, usually only after prompt and sometimes repeated exchange transfusions. This is the dimension of the problem that the gamma globulin treatment can eliminate.

In order to appreciate the importance of this new advance in preventive medicine, it may be helpful to review briefly the steps in the recognition and treatment of erythroblastosis fetalis due to Rh-incompatibility between mother and infant. Although the condition was described in its various forms during the previous 40 years, it was not considered an entity until 1932. The etiology remained obscure until 1939, when Levine, after studying a case of intragroup hemolytic transfusion reaction (a group O woman receiving a pint of her husband's group O blood), concluded that the patient who had just given birth to a stillborn infant with erythroblastosis fetalis must have become sensitized against a red cell factor in her baby which was inherited from its father. This brilliant and logical explanation stimulated further investigations of intragroup transfusion reactions. After 1941, when Landsteiner and Wiener published their studies on a new human blood type (the Rh system), its relation to the formerly mysterious transfusion reactions and especially to the development of erythroblastosis fetalis became evident. The entire field of immunohematology was stimulated to re-exploration and in the next dozen years or so another eight or nine independent families of blood group factors were uncovered. More than a hundred specific subtypes of these have now been described, and this has led to important advances in anthropology, legal medicine, transfusion therapy and homotransplantation.

Specific improvement in the management of erythroblastosis fetalis occurred with the development of new and more sensitive tests for Rh antibodies. The antiglobulin test of Coombs made the diagnosis of sensitization in the Rh-negative woman and erythroblastosis fetalis in her newborn infant entirely reliable. After 1946, it became possible to protect the live-born infant from the disastrous effects of severe hemolytic anemia through the use of exchange transfusion. This reduced the mortality from anemia and cardiac failure from 30 percent or more to a present level of 5 percent or less. The neonatal complication of jaundice from hyperbilirubinemia which so often resulted in kernicterus and death or, if less severe, in cerebral palsy, mental retardation or some specific nerve damage, with an incidence of over 20 percent, is now completely preventable.

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*Ortho Research Laboratories, Raritan, New Jersey.

Progress has also been made in the rescue of the one of five infants with severe erythroblastosis fetalis who might die *in utero* from cardiac failure and fetal hydrops. Amniocentesis yields fluid which is easily analyzed for its bilirubinoid pigment content. A high pigment level or a rising value on repeated taps has proven an accurate index of severe hemolytic disease *in utero*. Early delivery, if the thirty-fifth week of gestation has been reached, has saved some infants. For earlier gestational products, the bold approach first tried by Liley of New Zealand, consisting of intrauterine transfusion of the fetus via its peritoneal cavity, seems to be the only treatment available at present. From several medical centers where this is being practiced, the results indicate that 40 to 60 percent of fetuses with severe hemolytic disease can be rescued.

While the development of methods of treating erythroblastosis fetalis has led to satisfying alterations in its severity and outcome, the time required to care for each sensitized woman and to treat the affected infant (often with multiple exchange transfusions) has been formidable. The statistical incidence of sensitized Rh-negative women is between 1 and 1.5 percent. In California, with 350,000 births per year, even at the lower figure there would be 3,500 infants with erythroblastosis fetalis. This represents a significant pediatric case load. For the individual family in which a case has occurred and is likely to recur, it often means a serious financial burden, a dreaded psychological handicap and a limitation in family.

As proved lately in some 36 medical centers in the United States, and in an equally large number in Canada and in Europe, this worrisome disease can now be eliminated by the use of a single intramuscular injection of 1 ml of anti-Rh gamma globulin (RhoGAM®) containing 300 μgm of this antibody. When given to an Rh-negative unsensitized woman within 72 hours after delivery of an Rh-positive baby, this concentrate will block active immunization and thereby prevent erythroblastosis fetalis in the next pregnancy. The details of the experimental trial of anti-Rh gamma globulin concentrate in suitable cases have been reported previously by Freda, Gorman and Pollack of New York City in 1966 and by Clarke and his associates of Liverpool in 1967. Each group started independently to try to protect Rh-negative unsensitized women from immunization by their Rh-positive newborn babies. Their results were amazingly successful. In this country, the specific gamma globulin (RhoGAM®) was prepared under the supervision of Dr. Pollack of the Ortho Research Foundation of Raritan, N.J. This pharmaceutical laboratory supplied not only Freda and Gorman but 35 other groups of investigators all over the United States with their gamma globulin concentrate for trial use. The results to date, as compiled by Dr. William Ascari, Director of Clinical Research at the Ortho Laboratories, show that in almost two thousand cases where RhoGAM® was used, sensitization and anti-Rh production were prevented, whereas in more than a thousand cases in which no protection was used, sensitization developed in the expected number of about 7 to 8 percent.

Elsewhere in this issue of CALIFORNIA MEDICINE, Jennings and coworkers report experience with this concentrate at one of the 43 cooperating centers in the United States and abroad which tried RhoGAM®. Obviously a preventive treatment which promises almost 100 percent success in saving the Rh-negative unsensitized woman from immunization through pregnancy is an exciting development. It also becomes an important public health measure, since about 8 percent of childbearing women are at risk, according to Clarke's figures. Allowing for the number of women of Oriental and African background (predominantly Rh-positive) this figure might be reduced to 6.5 percent in California, yielding an estimate of about 20,000 each year who might need protection after childbirth.

The source of this concentrate is human plasma from sensitized Rh-negative men accidentally or deliberately given Rh-positive blood, or women also sensitized by transfusion or, much more commonly, by pregnancy. To compound the difficulty, the donors of this source plasma must have anti-Rh titers of 1000 or more whereas most titers are less than 50. To supply the need of California would require about 20,000 one-milliliter doses of the specific gamma globulin per year. This would demand a pool of about 1,300 liters of the high-titered plasma, or 5,200 donations of a pint of blood. Even if each donor were bled five times yearly, more than 1000 high-titered persons would be needed for California. Fortunately, the problem of donor procurement is not so formidable. By the technique of plasmapheresis, donors can be used every week or two and 500 ml of plasma can be harvested each time by withdrawing two pints of blood in sequence at each visit and returning the red cells immediately. By this method, a valuable donor can be the source of as much as 20 liters of plasma a year, so that 65 donors might supply the needed pool. However, restimulation of these anti-Rh serum producers through the use of injections of small amounts of Rh-positive cells would be necessary.

Considering the numerous difficulties already enumerated and several others not mentioned, the years of research and the free distribution of the product for clinical trial in thousands of cases, the present cost of $45 per milliliter for the commercial anti-Rh gamma globulin (RhoGAM®) is not unreasonable. At this rate, California would need to expend almost $1,000,000 for material alone. The necessary testing of each woman and her infant before using this prophylaxis would add to the cost per patient and this still would not include the cost of professional care.

To try to reduce this high cost of protection for Rh-negative women, departments of maternal and child health in several states are considering ways and means of procuring their own anti-Rh gamma globulin concentrate. The Division of Biologic Laboratories of the Department of Public Health of Massachusetts, with the participation and support of the Maternal and Child Health Department of the City of Boston, and in cooperation with the Blood Grouping Laboratory and the Children's Hospital in Boston, has already processed its first lot of serum and expects to be able to take care of its needs at a quarter of the cost of the commercial serum. Other public health departments should eventually be able to do likewise.

Whatever the cost, it is obviously necessary now to protect every woman who is at risk from Rh sensitization. Very likely we can expect that protection against Rh-sensitization will be practiced widely and soon. Numerous articles about it have appeared in state and national medical journals. In addition, a few feature stories about this important medical advance have been published in magazines, daily papers, and Sunday supplements. Rh-negative women are and will be demanding "the Rh serum" after delivery. Thus prompted, no physician can afford to be tardy in offering his patients the latest method of prophylaxis against Rh immunization. When prophylaxis is universally carried out, Rh disease or erythroblastosis fetalis a generation from now will be of historic interest only.

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A Word of Thanks

MOST PRACTICING PHYSICIANS have probably never heard of the Health Insurance Benefits Advisory Council (HIBAC). Its chronicle is recounted elsewhere in this issue. The government officials charged with the administration of Medicare (Title XVIII of the Social Security Act) have relied heavily upon advice sought and received from qualified persons outside of government. Many Californians are among those who have contributed their professional expertise both officially and unofficially.

We who work in the vineyards of medical practice are much in the debt of those of our members who have taken the time, first to become qualified in the technology of this complex field, and then to spend the countless hours it has taken to put their knowledge and experience to good use. It is we and our patients who have benefited, and we are pleased and proud to take this opportunity to commend those physicians who have undertaken this much needed yet essentially selfless task.

The President's Page

What Do the Dues Do?

"What do I get for the dues money I pay for affiliation with organized medicine"? This reasonable question is of interest to all physicians. The answer is a compound of answers.

The primary intraprofessional objective of organized medicine is to be the advocate for all physicians. Organized medicine, that is, the local, state and national organizations, performs three distinct functions:

1. Direct services.
2. Programs and projects designed to serve the physician and his patient.
3. The opportunity for the physician to serve his profession.

First, what are the direct services?

Availability of group insurance, accident and disability insurance and professional liability insurance are all usually available at more reasonable rates than if purchased individually. There are Keogh Retirement Fund programs, and the Physicians' Benevolence Fund which was created to provide financial aid to needy physicians and their families, and also legal counsel and advice concerning the practice of medicine.

Publications including the *Journal of the American Medical Association,* specialty journals, California Medicine and the excellent society bulletins are journals that cover the field of scientific medicine as well as socio-economic and current news related to medical practice. In addition, special newsletters and fact sheets are sent to our members which afford them the opportunity to be informed in all current aspects of professional activities.

A prime goal is to provide continuing medical education. This objective is accomplished by numerous courses, symposiums and seminars. The CMA publication *What Goes On* lists pages of medical education meetings designed to serve physicians in advancing the scientific practice of medicine.

Annual medical conventions highlight a wide variety of scientific presentations. The Audio-Digest Foundation provides tape-recorded summaries of national medical meetings and authoritative synopsis of current literature and papers presented in medical publications as a service to some 65,000 subscribers. Data on scientific or socio-economic subjects are made available in libraries maintained by our county societies, state associations and the AMA. The CMA socio-economic reports, the CMA's *Relative Value Studies* and opinions of the AMA Judicial Council on Medical Ethics are examples of the information available. The Physician Placement Service is another direct benefit.

Second, programs to advance the broad field of health care are made possible by your payment of dues. Funds are allotted for the activities of some 75 commissions and committees involving some 600 of your colleagues working under and reporting to the Council and House of Delegates. Both physician and patient benefit. For example, the Hospital Survey Teams' activity reviews the work of hospital medical staffs to insure the highest quality of health care. In addition, numerous immunization programs are maintained, programs for round-the-clock emergency medical care are established, and guidelines for utilization and review work in hospitals and for extended care facilities have been developed.

In medical socio-economics we have helped to establish improved health insurance programs with broader benefits for our patients. We are establishing better methods for the provision and delivery of health care. Peer review committee activity is a most significant work being done on adjudication of claims. We constantly strive to improve government medical programs. In the field of mental health, better patient care was achieved through our CMA inspection team report on California mental institutions. We are working to improve Medi-Cal and we have established the concept of mainstream medical care for all. We upgraded the Workman's Compensation law and the CHAMPUS program (dependents of servicemen).

Organized medicine provides a direct liaison with the executive and legislative branches of medicine on all government levels. It introduces and sponsors legislation in behalf of the public and the profession.

Another endeavor is to communicate medical activities to the public. Pamphlets, film strips, movies, speakers bureaus and medical news for the news media are ways in which organized medicine informs and educates the layman.

Third, opportunity for the physician to serve his profession. Long gone is the day when a few elder physicians could "run" a medical society. Organized medicine needs the involvement of all physicians. We need all of the various medical disciplines; we need all the specialties. We need the involvement of the academic physician, the public health physician, the solo practitioner and the group practitioner, the industrial physician as well as the research physician—we need all the segments of our profession.

To participate is to recognize a unity of purpose to improve all aspects of health care. To participate is to carry one's share of the load and fulfill the inherent responsibility of being a physician.

Our associations benefit us to the extent that they provide an arena for our active participation to maintain and advance the art and science of medicine. And, to achieve these goals, we prudently expend the physician's dues monies.

Finally, it is only through attending and paricipating in medical association activities that your money keeps you informed on society affairs, helps develop solutions to the problem of our profession, and helps achieve a resolution of the many problems related to government and the public.

Malcolm C Todd, MD

SUGGESTIONS FOR FENDING OFF CARDIAC ARREST

"[Four practical suggestions for minimizing the chance of cardiac arrest:] Do routine measurements of blood gases and maintain optimal control of airways and ventilators; give primary attention to underlying causes of failure, which—if uncorrected—progress to severe metabolic acidosis and shock; avoid single central venous injection of drugs; and until more is known, exclude aminophylline from the armamentarium of your clinical care facility."

—Samuel J. Camarata, M.D., Orange

Extracted from *Audio-Digest Anesthesiology,* Vol. 10, No. 20, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

LETTERS *to the Editor*

Drug Interactions

To the Editor: The excellent review article by Morelli and Melmon in CALIFORNIA MEDICINE 109:380-389, Nov., 1968, on "The Clinician's Approach to Drug Interaction" calls attention to some often-overlooked aspects of polypharmacy. In such a comprehensive review within limited space, it is probably inevitable that at least one error should be found; this "letter to the editor" calls attention to one.

The authors say ". . . indomethacin may cause bleeding in patients taking coumarin anticoagulants." The reference given to justify this statement (Hoffbrand and Kininmouth, Brit. Med. J. 2: 838-839, 1967) specifically states that the patient described therein developed hemorrhagic complications while on phenylbutazone and not "while taking indomethacin." The British authors nevertheless reasoned—by analogy with phenylbutazone—that indomethacin *might* produce a similar effect.

The folly of reasoning by analogy is seen by further examination of the literature; the possibility of interaction between indomethacin and anticoagulants has occurred to others, and several publications exist, specifically devoted to investigation of the effects of indomethacin in patients on anticoagulant therapy. Müller and Zollinger in "Die Entzündung — Grundlagen und Pharmakolische Beeinflussung" (a symposium volume published by Urban & Schwarzenberg, Munich, Berlin, Vienna, 1966) compared 14 patients on oral anticoagulants with indomethacin with 14 patients on the same anticoagulants without indomethacin. They concluded (freely translated): "Indomethacin may be given without any further precautions to patients on anticoagulants."

Identical conclusions were reached by Frost and Hess (in the same volume), by Müller and Herrmann, Medizinische Welt 17:1553-1554, 1966, and by Gáspárdy, Balint and Gáspárdy, Zeitschr. für Rheumaforschung 26:332-335, 1967. No contrary results by any clinician who has actually tried indomethacin in patients on anticoagulant therapy have come to my attention.

The regrettable thing about unsupported statements is that they become perpetuated in the literature, and the corrections never quite catch up with the errors. So maybe it is inevitable that the statement made in the review will be added to the already formidable list of misconceptions — many of them unfavorable — about this particular drug.

Incidentally, Morelli and Melmon omitted mention of indomethacin in their list of drugs, Appendix B, supposedly listing all generic and trade names mentioned in their review.

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The Author Replies

Professor Winter is quite correct that the evidence attributing hemorrhagic complications to combined therapy with coumarin anticoagulants and indomethacin is tenuous, at least on the basis of direct interactions. The authors would maintain, however, that circumspection would be appropriate when administering anticoagulants to a patient receiving a drug reported to cause gastrointestinal bleeding. Perhaps in this context the attribution is not entirely inappropriate in an article designed to emphasize the multiplicity of drugs and potential mechanisms of direct and indirect interaction of potential clinical importance. We do regret any misleading implications our statement may have.

Thank you for permitting us to review Professor Winter's letter. We are grateful for his comments.

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Anti-Rh Immune Globulin: How Should We Use It?

To the Editor: A few months ago a reliable pharmaceutical house put on the market a potent preparation of anti-Rh$_0$ (D) gamma globulin (IgG) for the prevention of Rh immunization by pregnancy.* Many independent studies have demonstrated that 1 ml (300 mcg) of this material, given intramuscularly to an Rh negative woman within 72 hours after she delivers an Rh positive child, almost invariably prevents primary immunization to the Rh factor. It now seems clear that widespread use of such material will eventually all but wipe out hemolytic disease of the newborn due to Rh incompatibility.

Almost immediately following the appearance of this new product, the legal counsel of the California Hospital Association issued a warning to all member hospitals and their staffs that the failure of a physician to provide such treatment may leave him open to suit. Further, he urged that patients who refuse this treatment for any reason be asked to sign a legal waiver, the facts being documented in the hospital record. His statement implied strongly that this agent has thoroughly proven itself, and that no further research is needed.

As a matter of fact, the indications for the use of Rh immunoglobulin, and the correct dose under various conditions, remain by no means clear. For instance, neither the counsel's statement nor the brochure distributed with the immunoglobulin refers to ABO group of mother and child, although it is widely known that ABO compatibility plays a crucial role in the mechanism of Rh immunization, and in spite of the fact that only ABO compatible pregnancies were included in the experimental studies on this new product. Levine[1] in 1943 reported that group O, Rh negative women with group AB, Rh positive husbands almost never develop Rh antibodies due to pregnancies alone, presumably because their fetuses are all of *incompatible* ABO group. Prokop[2] failed to stimulate the production of Rh antibodies in Rh negative volunteers by injecting Rh positive blood of incompatible ABO group. Stern et al,[3,4] in a similar experiment, found a few such volunteers who did develop Rh antibodies, but the percentage was small, and the antibodies invariably of low titer. Furthermore, they injected much larger volumes of Rh positive blood than normally reach the maternal circulation during pregnancy and delivery. The question as to whether Rh negative women are *ever* immunized against the Rh factor by *uncomplicated* ABO incompatible pregnancies must remain in some doubt.

On the other hand, 1 ml of anti-Rh immune globulin may at times prove entirely inadequate. Woodrow[5] and his colleagues in Great Britain demonstrated that the likelihood of Rh immunization in ABO compatible pregnancies is directly proportional to the amount of fetal blood reaching the maternal circulation. There are at least two reports[6,7] of five Rh negative women who promptly developed Rh antibodies after delivering an Rh positive baby in spite of receiving injections of more than the recommended 300 mcg of immunoglobulin. Failure of the globulin to prevent immunization was presumably due to the very much larger than normal amounts of fetal blood in the circulation of these women, ranging in estimated volume from 60 to 350 ml. Woodrow et al[8] estimate that in one of every 300 deliveries, transplacental hemorrhage of over 100 ml occurs. Correspondingly, the British group has redesigned their study on the basis of Kleihauer tests of the mothers' blood after delivery, giving 1 ml of anti-Rh immunoglobulin when there is evidence of a fetal-maternal bleed of less than 0.25 ml, and giving 5 ml in case of larger fetal hemorrhage.

It is obviously much too early, therefore, to lay down, under threat of legal action, blanket rules regarding the use of Rh immunoglobulin in the prevention of Rh immunization. Rules of thumb, such as those issued by the manufacturer should serve only as a guide. Only after much more research and observation will the indications for this agent, and the best dose under various circumstances become entirely clear.

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*RhoGAM®, Ortho Pharmaceutical Corp., Raritan, New Jersey.

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Keeping Abreast of Inflation

To the Editor: As inflation presses faster upon us it is time the physicians of California devoted some more detailed study to the inflationary way of life.

One basic feature of inflation is that there is no longer a fixed value to the currency. This was assured by the shift to a fiat currency this past year. Thus if you evaluate an object or service rendered in dollars you must recognize that it is the dollar of the moment in which you are speaking. If you wish to compare to the value at another time, those current dollars must be converted. At present the Consumer's Price Index of the U.S. Bureau of Labor Statistics seems to afford the most widely used dollar value comparator.

In the practice of medicine we can evaluate our services in units. This unit has a definite fixed standard (*i.e.* one office visit, one-fourth hour of anaesthesia, or whatever suits your practice). This evaluation in units remains the same from year to year. To understand inflationary pressures on your income the units of service rendered, the unit value in dollars of the present or projected time, and the value in dollars in a base time period all need to be considered.

The table shown provides one such comparison. The underlined figures in the table show the relationship between spendable income in 1960 with a unit value of $5.00 and the spendable income in 1968 with a unit value of $7.00. Any one can work out his own table for his own units of income. It should be noted that in most practices the cost of doing business has increased at least 50 percent and often up to 75 percent since 1960. Thus a 10,000-unit service performance in 1960 may have broken down to 4,200 units for business expense and 800 units for deductible personal expenses. If your units of service performed are the same in 1968 as in 1960 and you have raised your unit value from $5.00 to $7.00, you would have money to cover a $10,000 increase in business expense and deductible personal expenses. If, however, you had an actual increase of $15,000 instead, you needed a unit valuation of $7.50 to just about break even in the comparison of 1968 spendable income with 1960.

This, of course, allows no increase in compensation for any greater knowledge and proficiency

	Married, two dependents						*Unmarried*	
Units earned (see below)	5,000	5,000	6,000	6,000	7,000	7,000	5,000	5,000
Unit Value	$5	$7	$5	$7	$5	$7	$5	$7
Gross in 1960 Dollars	$25,000	$35,000	$30,000	$42,000	$35,000	$49,000	$25,000	$35,000
Tax in 1960	6,808	11,806	9,146	15,764	11,806	18,924	11,916	17,840
Net Spendable Income, 1960	18,192	23,194	20,854	26,236	23,194	30,076	13,084	17,160
Tax in 1968	7,226	12,073	9,471	16,050	12,073	20,405	11,101	17,748
Net Spendable Income, 1968	17,774	22,927	20,529	25,950	22,927	28,595	13,899	17,252
Ditto in 1960 Dollars (80¢)	14,219	18,342	16,423	20,760	18,342	22,876	11,119	13,802
Net spendable income from next dollar earned in 1960 Dollars (80¢)	47½¢	38½¢	43½¢	36¢	38½¢	32¢	22½¢	28¢

Units earned represent the units available as spendable income (before taxes) after the units spent as business expense and personal deductions have been removed. Any increase in these two items beyond the increase afforded by unit value change would necessitate an overall increase in the number of units of service performed and collected. The underscored figures relate the net spendable income in 1960 and 1968 to a constant purchasing power.

Note: The valuation of 1968 dollars as 80 cents in terms of 1960 dollars is as projected on December 31, 1968. As of October, 1968, it is approximately 81 cents.

in public service that eight years may have developed in you. It also allows no compensation for the loss in purchasing power of any money you may have had invested to yield less than 4.5 percent after taxes during 1968.

It is to be hoped that each physician will look carefully at the problems of inflation. He should put his house in shape to keep available to him that share of spendable income he may have become accustomed to receiving. He should pressure his leaders in the CMA to keep fees not only usual and customary but also *timely*. Certainly tolerance of cut rates in Medicaid, Compensation, Medicare, and State Finance Department cases is opening the floodgates to a rather shocking reduction in your spendable income when the final phases of the Wagner-Murray-Dingell Bill are enacted by Congress.

E. KENNETH SMITH, M.D.
Eureka

"Acute Renal Failure Due To a Bismuth Preparation"

To the Editor: Your "Letters to the Editor" section recently (Calif. Med., Dec. 1968, pages 521-522) featured an exchange of views between Dr. Murray C. Zimmerman and Dr. John A. James, in which Dr. Zimmerman took exception to Dr. James' position on the use of an oral bismuth preparation (Bistrimate®) as documented by Dr. James in his paper "Acute Renal Failure Due to a Bismuth Preparation" (Calif. Med., Oct. 1968, pages 317-319). In presenting his own ideas on the subject, Dr. Zimmerman stated "In the Los Angeles area, Dr. James could either run this through MEDLARS data retrieval computer at UCLA, or use the cheaper and more efficient older model data retrieval device, produced by unskilled labor and with no repair, maintenance or amortization cost known as the "George X. Trimble."

Although I am not especially well informed about what the internal problems of UCLA MEDLARS happen to be at the moment, I can with some authority say that Dr. Zimmerman is not entirely accurate in his characterization of my filing system, for one segment of the unskilled labor division recently had to have some maintenance work in the form of an appendectomy while another is scheduled for some dental repair. Notwithstanding the limitations that such strictures impose on the efficacy of our medical information storage and retrieval project, I would nevertheless like to rise to the occasion and submit some comments which may be helpful in reconciling the disparate views of the above-mentioned respondents.

I would not take issue with Dr. James' introductory statement in his paper, to wit, "It is well known that the salts of bismuth are toxic to the kidney." It should be noted, however, that much of the documentation that supports this thesis deals with parenteral bismuth preparations. Nor shall I comment on the validity of the summary of his paper, which starts out, "A case of acute renal failure in a 14-year-old girl due to an oral bismuth preparation is reported"—a conclusion which Dr. Zimmerman considers unwarranted, and "not proved."

I do, however, want to direct attention to that part of Dr. James' reply which reads, "This drug (bismuth sodium triglycollamate [Bistrimate]) was implicated in two of the recent cases of acute bismuth nephrotoxicity cited in the case report." Lest the true nature of this implication not be clearly understood, I feel it should be pointed out that in the one case the patient, an 8-year-old girl, ingested some 250 tablets of Bistrimate (each containing 75 mg of elemental bismuth) over a four-month period. In the other case the patient, a 19-year-old girl, ingested in presumably a brief period of minutes or seconds, 21 tablets of Bistrimate (equivalent to 1,500 mg of elemental bismuth). Thus, it should be clearly understood that at least in these two cases the toxic effects were related to a dosage well in excess of the therapeutic range. By comparison the patient described by Dr. James in his paper took over a period of a few hours "7 or 8 pain pills" which were later identified as tablets of Bistrimate, each containing 75 mg of elemental bismuth. While the dosage in this instance exceeds that recommended by the manufacturer, it is still considerably less than the dosages involved in the above-mentioned cases. This distinct difference in dosage would tend, in my estimation, to raise some doubt as to whether the reaction described by Dr. James was actually due to the oral bismuth preparation.

GEORGE X. TRIMBLE, M.D.
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Role of the Intra-Atrial Electrogram in the Clinical Interpretation of Arrhythmias

JOHN W. LISTER, M.D.

Material Supplied by the California Heart Association

IRREGULARITIES OF THE cardiac rhythm are a common phenomenon in patients with heart disease. The prompt treatment of an arrhythmia is facilitated by the exact diagnosis of the abnormal rhythm. The key to arrhythmia diagnosis is the determination of the temporal relationship between atrial and ventricular activation.

During many tachycardias atrial activity (P waves) frequently can not be seen on the standard lead surface electrocardiogram; consequently, it may be difficult or impossible to determine the origin of a tachycardia, i.e. sinus, atrial, A-V nodal or ventricular. Recording of the right intra-atrial electrogram, clearly defines the atrial rhythm, and the temporal relationship of atrial to ventricular activation.

An electrode wire or a standard bipolar electrode catheter, with electrodes 1 cm apart, can readily be passed into the right atrium via a needle puncture of the femoral vein or surgically exposed anticubital vein. From an electrode wire a unipolar intra-atrial electrogram can be obtained, and from a bipolar catheter a unipolar and bipolar intra-atrial electrogram can be recorded.

The unipolar intra-atrial electrogram is recorded by connecting an intra-atrial electrode to the V lead of the electrocardiograph machine. The unipolar electrogram records the entire electrical sequence of P wave and QRS complex, and magnifies the size of the P wave. The bipolar intra-atrial electrogram is obtained by connecting one intra-atrial electrode to the right arm lead and the other intra-atrial electrode to the left arm lead of the electrocardiograph machine, and recording on Lead I. The bipolar electrogram primarily records the time of arrival of the atrial impulse in the area of the electrodes, and accurately delineates the timing of the P wave in the cardiac cycle. In the bipolar electrogram, the ventricular component (QRS complex) is usually a minor component or not present on the tracing. When the QRS complex and P wave are simultaneous, the time of atrial activation is clearly depicted by the bipolar intra-atrial electrogram. In most instances, atrial activity can be clearly delineated by the unipolar electrogram. However, not infrequently, the P waves are buried in the QRS complex or T waves, and the unipolar intra-atrial electrogram does not permit a clear definition of the rhythm. In these cases, recording of the atrial rhythm by the use of the bipolar electrogram clarifies the rhythm.

In our experience, the recording of unipolar and bipolar intra-atrial electrograms has been an important aid in the diagnosis of arrhythmias. In cases of atrial flutter and tachycardia the ventricular rate is easily determined from the standard electrocardiogram, but frequently the atrial rate cannot be ascertained. The intra-atrial electrograms clearly show the atrial rate. Thus, the degree of block at the atrioventricular node can be determined. Knowledge of the degree of A-V junctional block is often helpful in deciding upon the mode of treatment of an arrhythmia.

We have had a number of cases in which repeated electrocardiograms have been interpreted as sinus tachycardia with first degree atrioventricular block. However, upon the recording of intra-atrial electrograms these rhythms were shown to be atrial tachycardia with 2:1 A-V block. In one of these cases, the electrocardiogram was interpreted as sinus tachycardia with first degree heart block and incomplete right bundle branch block. There was an R′ in the QRS complex in leads V1 and V2. The unipolar electrogram did not clarify the rhythm, but the bipolar electrogram clearly showed atrial tachycardia with 2:1 A-V block and the R′ in leads V1 and V2 was not due to an intraventricular conduction defect but a P wave superimposed on the end of the QRS complex.

The recordings of intra-atrial electrograms have clarified the rhythm in five cases of tachycardias with irregularly irregular ventricular rates, which did not slow after the administration of relatively large doses of digitalis. Three of the above five arrhythmias had been interpreted as atrial fibrillation with a rapid ventricular response from standard lead electrocardiograms. In one case, atrial

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Dr. Lister is Chief, Section of Electrophysiology, Division of Cardiology, Department of Internal Medicine, Mount Sinai Hospital of Greater Miami, Miami Beach, Florida.

fibrillation with a rapid ventricular response was present; in two cases, atrial tachycardia with variable A-V block was present; and in two cases, a wandering atrial pacemaker with an irregular atrial rate and varying A-V conduction was present. The clarification of these arrhythmias facilitated their treatment.

In two cases of tachycardia, the ECG showed a regular rate and aberrant ventricular activation. On auscultation the first heart sound was of constant intensity. From these findings it could not be clearly established whether these were supraventricular or ventricular tachycardias. The intra-atrial electrograms revealed that one case was a ventricular tachycardia with atrial fibrillation and the other case was ventricular tachycardia with atrial standstill. The diagnosis of the arrhythmias facilitated their prompt treatment. These cases also demonstrated that the constant intensity of the first heart sound does not rule out ventricular tachycardia.

In A-V nodal rhythms and in certain instances of A-V dissociation, atrial activity may be obscured by the QRS complex. The recording of intra-atrial electrograms will clarify these rhythms. In A-V junctional rhythms there may be A-V dissociation, retrograde activation of the atria, or retrograde A-V block. In A-V dissociation there is a beat-to-beat change in the temporal relationship between atrial and ventricular activation, because the atria and ventricles are beating independently of each other. When retrograde atrial activation is present there is usually a fixed temporal relationship between ventricular and atrial depolarization. In cases of A-V junctional rhythms with retrograde A-V block the atria are either beating slower than the ventricles or atrial standstill may be present. The specialized conduction system of the heart is a two-way conducting system. Therefore, in the presence of A-V dissociation, when the atria are beating at a significantly greater rate than the ventricles, antegrade A-V block is present. When the atria and ventricles are beating independently of each other at about the same rates (isorhythmic A-V dissociation), a functional rather than a pathologic block is usually present at the A-V node. When the ventricles are beating at a faster rate than the atria retrograde A-V block is present.

In complex arrhythmias, the recording of unipolar and bipolar intra-atrial electrograms always depicts the temporal relationship between atrial and ventricular activation. The delineation of the time relationship of atrial to ventricular depolarization is an important aid in arrhythmia diagnosis and treatment.

The Second National Congress On Medical Ethics

WILLIAM A. BELLAMY, M.D., *San Francisco*

ESCALATING RATE OF change in practices of Medicine, and the interest and active participation in Medicine on the part of interested citizens not necessarily possessing professional training, were primary themes recurring throughout the American Medical Association's Second National Congress on Medical Ethics held October 5 and 6 in Chicago. Only three years passed between the first national congress and the need to hold the second one. The AMA estimates that a Third National Congress on Medical Ethics may be needed as early as 1970.

Our current ethical dilemmas stem from innovations such as: cracking the genetic code so that man now possesses the power to tamper with heredity. But who will decide in which direction an individual's heredity is to be changed? Or how extensively should artificial insemination be utilized? In connection with organ transplant, what criteria of death are most reliable? And what about euthanasia, still recommended by some persons? By what criteria may it be determined when an organ for transplant may ethically be taken from a doner? And who decides what recipient is to live (with a donor organ) and which person is to be left to die? Medical innovations such as organ transplants or kidney dialysis are very costly. Who is to decide whether the available capital is better spent for transplants, dialysis, or food for the starving? These questions were dealt with at the second national congress.

"Medical Ethics always has been primarily for the benefit of the people and secondarily for the benefit of Medicine," said Chauncey D. Leake, Ph.D., Sc.D., of the University of California, San

Francisco. The current momentous problems mentioned above, of necessity will require the best intelligence of many elements in our society—judiciary, social scientists, clergy, political planners, and all interested citizenry in our highly literate, enlightened society.

However, "a monolithic code of ethics is not adequate," said Dr. Leake. "Enlightened people vary in their opinions as to what is right or wrong. Ethical decisions can be made on the basis of an individual situation."

A physician must not isolate himself from the ever-widening problems of today. "He, as a citizen, has an ethical responsibility to participate in discussions [of the subjects related to ethics] especially when man seeks answers as to their rightness or wrongness," said E. G. Shelley, M.D., chairman of the AMA Judicial Council. "In man's never-ending search for the truth," the physician must consult with many other disciplines in society.

Truth is valuable only insofar as it is used. The physician "owes patients the truth as fully and as honestly as owing skill and proper care," said Dr. Leake. Members of all professions owe it to society to present their expert knowledge in simple, understandable language. "It may then be possible," Dr. Leake continued, "with recognition of the various ethical principles involved, to get the public understanding and support that will help to use our technical triumphs in worthy ways for individual and social welfare."

Dwight L. Wilbur, M.D., President of AMA, acknowledged that Medicine needs to utilize the expertise of other disciplines, but urged the imperative that the physician fulfill his rightful place as consultant to social planners. Dr. Wilbur expressed a farsighted prophecy that "eventually the world will need an International Code of Ethics, and this will demand of all of us the utmost in cooperation."

"Man dies in stages," said Frank J. Ayd, M.D., Fellow of the American Psychiatric Association. He defined: (1) clinical death, in which a person is dying but life can be restored; (2) brain death, in which the brain is dead and therefore all integrated functioning of organs ceases and the body is dead; (3) death of the component organs of the body, followed still later by death of tissue cells of bodily organs.

In the state of clinical death, to permit a person to die is euthanasia. Dr. Ayd believes such a person should be kept alive with respirators or other measures, even though he is no more than "a vegetable."

In brain death, we know how to keep the organism "alive" but this is senseless. Quoting Sir Theodore Fox, "We shall have to learn to refrain from doing things merely because we know how to do them." Dr. Ayd said that he believes taking an organ from a person in a state of brain death is morally right, and that by transplanting this organ in a dying recipient "we are helping others to live" — the primary objective of Medicine throughout written history. Thus, Dr. Ayd disagrees with Pope Pius XII, who said physicians "are directly disposing of the life of the patient." Fortunately, the courts in most instances have ruled that the physician had not practiced euthanasia in such cases. Dr. Ayd believes that in time "brain death" will be made synonymous with "legal death" and that the advent of organ transplantation impells new definitions of our ancient concepts of death. "We want our fellow men to know that we are just as desirous of safeguarding the right of the dying as we are of helping others to live. This is why we have adopted new criteria of death," Dr. Ayd said.

Although it may be difficult to do so, death can be defined, while "who shall live" inevitably remains a value judgment and can never be defined. Yet, with limited equipment for kidney dialysis, somehow it must be determined who among the dying will receive dialysis and who will be left to die. The "Seattle Plan" proposes that a committee make social judgments, such as Mr. A gets drunk and has children while Mr. B does not get drunk but is childless.

Paul A. Freund, S.J.D., Professor of Law at Harvard University, deplores such social judgments. Reporting a discussion on the "Seattle Plan," Dr. Freund said: "They took the case of a man with a family, and on the other hand a derelict prostitute. Surely you wouldn't have any trouble choosing between them." Dr. Freund quipped, "Well, how do you know how she became a prostitute? The man with a family may have contributed to her present state."

Rather than social judgments, Dr. Freund suggests consideration be given to the younger, medical screening of those with a better chance to live, by first-come, first-served, or by lottery.

In summary, ethical problems have always been with us, and matters of right and wrong continually change. As stated by Robert B. Hunter, M.D., Sedro-Woolley, Washington: "At one time it was moral and legal to have slaves. Now the opposite is true." In matters of ethics, pooling of expertise, the people's opinions and desires, social planning —all must filter through the ethical conscience of each individual contributor. The present Principles of Medical Ethics of AMA have been modified over the years, especially the annotations which stand the test of time less sturdily than do the broad general truths expressed in each of the ten principles and preamble of this document. The AMA, through its Judicial Council, welcomes the opinions of all interested citizens and readily will modify further the AMA Principles of Medical Ethics to meet current and future needs. The National Congresses on Medical Ethics contribute greatly toward this goal.

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See Detailed Program Following Page 106 in January issue

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Department of Pediatrics
School of Medicine
Director, Health Resources Study Center
University of Washington

ROBERT D. BLOODWELL, M.D.
Chief of Pediatric Surgery Section
Department of Surgery
Assistant Professor of Surgery
Baylor University College of Medicine

BARTON CHILDS, M.D.
Professor of Pediatrics
Johns Hopkins University
School of Medicine

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Mayo Clinic
Professor of Neurology
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In Memoriam

HARRY H. WILSON, M.D.
1892-1968

A physician can be judged as a man by using two criteria. First is he competent and successful in the medical care of his patients? Second is he recognized by his professional medical fellows as a leader dedicated to the profession of medicine and is he then given the privilege to lead it in perilous times? In addition to having many attributes of worth, Harry H. Wilson was such a man.

Harry H. Wilson was born 6 February 1892, and died, of Hodgkin's disease, 4 December 1968. Dr. Wilson was graduated from the Medical School of the University of Illinois in 1916. He was a member of N.S.N. and A.O.A. He then served as an intern and resident at the Los Angeles County General Hospital. He began practice as a specialist in internal medicine. He conducted himself as a gentleman and was successful as a physician. His social and business contacts were respected. As a sportsman he was well known as a polo player of ability. He was well equipped in many capabilities.

In the depression years of the '30s, the profession of medicine encountered many problems. Countless groups of new citizens came to California from "dust bowl" areas and created problems in welfare care, especially as related to medicine. Also many physicians from other states came to California, some of them to retire, others to practice "just a little." Among them were physicians who had been trained many years before under lower standards of education or had been imbued with varying ideals of ethics. This created problems. In addition several ill conceived and impractical plans for the solution of all problems of medical care were espoused politically. Thanks to the efforts of Harry Wilson and others at that time, the standards of medicine were kept high.

Harry Wilson later became President of the Los Angeles County Medical Association, then a Councillor of the California Medical Association and a Delegate to the American Medical Association. He was elected President of the California Medical Association and was one of the wise men who guided medicine in California through the difficult years of World War II. His services to his profession should not be forgotten.

E. Vincent Askey, M.D.

Bradby, Sanford Pearl, Jr., Fort Sill, Oklahoma. Died 13 November 1968, aged 35. Graduate of Meharry Medical College, Nashville, 1956. Licensed in California in 1961. Doctor Bradby was a member of the Los Angeles County Medical Association.

⁂

Callan, Martin Beil, Modesto. Died 2 December 1968 in Modesto of leukemia, aged 42. Graduate of University of Minnesota Medical School, Minneapolis, 1950. Licensed in California in 1953. Doctor Callan was a member of the Stanislaus County Medical Society.

⁂

D'Alessio, Joseph Anthony, Seal Beach. Died 6 December 1968 in Los Angeles of severe hypertension, aged 66. Graduate of Hahnemann Medical College and Hospital of Philadelphia, 1930. Licensed in California in 1931. Doctor D'Alessio was a member of the Los Angeles County Medical Association.

⁂

Elliott, James Wagner, Placerville. Died 7 December 1968 in Sacramento of hepatitis, aged 50. Graduate of University of Southern California School of Medicine, Los Angeles, 1945. Licensed in California in 1945. Doctor Elliott was a member of the Sacramento County Medical Society.

⁂

French, Richard Louis, North Hollywood. Died 2 January 1969 in North Hollywood of coronary artery disease, aged 60. Graduate of University of Southern California School of Medicine, Los Angeles, 1936. Licensed in California in 1936. Doctor French was a member of the Los Angeles County Medical Association.

⁂

Gray, Earl Haskins, Pacific Grove. Died 12 December 1968 in Pacific Grove, aged 66. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1929. Licensed in California in 1929. Doctor Gray was a retired member of the Yolo County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

⁂

Hollingsworth, Merrill W., Santa Ana. Died 11 December 1968 in Orange, aged 78. Graduate of the University of California Medical School, Berkeley-San Francisco, 1917. Licensed in California in 1917. Doctor Hollingsworth was a member of the Orange County Medical Association.

⁂

Howard, Merildeen W., North Hollywood. Died 16 December 1968 in Burbank of heart disease, aged 57. Graduate of Wayne University College of Medicine, Detroit, 1939. Licensed in California in 1946. Doctor Howard was a member of the Los Angeles County Medical Association.

JOHNSTONE, FRANK CHIEL, South Pasadena. Died 12 December 1968 in South Pasadena of arteriosclerotic heart disease. Graduate of Jenner Medical College, Chicago, 1911. Licensed in California in 1939. Doctor Johnstone was a member of the Los Angeles County Medical Association.

⁂

MICHALS, N. J., Lodi. Died 29 November 1968 in Lodi of cerebral vascular accident, aged 76. Graduate of College of Medical Evangelists, Loma Linda-Los Angeles, 1928. Licensed in California in 1928. Doctor Michals was a retired member of the San Joaquin County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

⁂

PETERSON, FLOYD RUSSELL, Los Angeles. Died 21 December 1968 in Los Angeles of coronary occlusion, aged 50. Graduate of the University of Minnesota Medical School, Minneapolis, 1943. Licensed in California in 1947. Doctor Peterson was a member of the Los Angeles County Medical Association.

⁂

PRICE, CURTIS LEE, Chula Vista. Died 12 December 1968 in Los Angeles, aged 49. Graduate of George Washington University School of Medicine, Washington, D.C., 1953. Licensed in California in 1954. Doctor Price was a member of the San Diego County Medical Society.

⁂

RAMSEL, CECIL LEWIS, Lodi. Died 1 January 1969 in an airplane crash near Lodi, aged 43. Graduate of University of Utah College of Medicine, Salt Lake City, 1956. Licensed in California in 1960. Doctor Ramsel was a member of the San Joaquin County Medical Society.

⁂

SHARP, JACK M., Santa Cruz. Died 30 November 1968 in Santa Cruz, aged 56. Graduate of Ohio State University College of Medicine, Columbus, 1938. Licensed in California in 1946. Doctor Sharp was a member of the Santa Cruz County Medical Society.

⁂

SHORT, JOHN EDWARD, Los Angeles. Died 6 January 1969 in Los Angeles of coronary artery disease, aged 67. Graduate of Temple University School of Medicine, Philadelphia, 1932. Licensed in California in 1933. Doctor Short was a member of the Los Angeles County Medical Association.

⁂

SHIPOUNOFF, GEORGE C., Oakland. Died 4 January 1969 in Oakland, aged 51. Graduate of University of California Medical School, Berkeley-San Francisco, 1944. Licensed in California in 1944. Doctor Shipounoff was a member of the Alameda-Contra Costa Medical Association.

⁂

VAN DER REIS, MAURITS, San Francisco. Died 18 December 1968 in San Francisco, aged 69. Graduate of Rijks-Universiteit te Groningen Medische Faculteit, Netherlands, 1924. Licensed in California in 1953. Doctor Van Der Reis was a member of the San Francisco Medical Society.

⁂

VITTRUP, JOHN F., Costa Mesa. Died 27 December 1968 in Alexandria, Va., aged 35. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1956. Licensed in California in 1965. Doctor Vittrup was a member of the Orange County Medical Association.

⁂

WHITE, EARL L., San Francisco. Died 25 December 1968 in San Francisco, aged 62. Graduate of University of California Medical School, Berkeley-San Francisco, 1934. Licensed in California in 1935. Doctor White was a member of the San Francisco Medical Society.

⁂

WHITECOTTON, GEORGE OTIS, Berkeley. Died 16 December 1968 in Oakland of heart disease, aged 70. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1933. Licensed in California in 1933. Doctor Whitecotton was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

⁂

WILKINS, ROBERT F., Los Angeles. Died 23 December 1968 in Gardena of acute bacterial endocarditis, aged 59. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1943. Licensed in California in 1943. M.D. degree from California College of Medicine, 1962. Doctor Wilkins was a member of the Los Angeles County Medical Association.

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

WOMAN'S AUXILIARY

to the California Medical Association

AMA-ERF

THIS IS THE YEAR! Doctors are being bombarded through their medical news media to give to AMA-ERF. WHY AMA-ERF? The foundation of medicine is education and research. The American Medical Association established and underwrites AMA-ERF to foster this cause. AMA-ERF currently sponsors six programs: Funds for Medical Schools, the Loan Guarantee Program, The Institute for Biomedical Research, Program in Medical Journalism, Project on Tobacco and Health and Research Grants Program. As Auxiliary members we pledge our financial support to Funds for Medical Schools and The Institute for Biomedical Research.

The Woman's Auxiliary to the California Medical Association contributed $54,965.02 to AMA-ERF this past year with Los Angeles County raising $22,946.41 of this amount. The California Medical Association can be proud of its Auxiliary, as this was the most money raised by any one state or county auxiliary in the United States. An innovation, a red ribbon award, was begun in California to honor the county and district auxiliaries that donate $10 or more per member. Red ribbon counties and districts for 1967-68 were as follows: Imperial, Kern, Los Angeles, Los Angeles Districts 1, 6, 9, 10, 11, Orange and San Luis Obispo.

Dr. Dwight L. Wilbur, American Medical Association President, is urging every physician to give $100 or more to the Funds for Medical Schools of AMA-ERF or contribute directly to the medical school of their choice. Given through AMA-ERF, your money makes a larger impact as a donation directly from medicine. With the reduction in federal research and training programs, medical schools desperately need this help from the medical family. Have you given your $100 or more yet? Give your Auxiliary member wife your check today . . . not only is it tax deductible but it might help her county or district auxiliary earn a red ribbon!

MRS. WARD L. HART
AMA-ERF State Chairman

PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H.
Director, State Department of Public Health

Cancer in California—New Developments

AN ESTIMATED 32,000 new cases of cancer will occur in the three-year period 1969-1971 in five Bay Area counties, if predictions made in advance of the Third National Cancer Survey, which is soon to begin, are borne out.

In this survey under the sponsorship of the National Cancer Institute, medical schools, medical associations, health departments, voluntary health agencies and other organizations will study a representative cross-section of communities across the nation. Included is the San Francisco-Oakland Standard Metropolitan Statistical Area, comprising San Francisco, Alameda, Contra Costa, Marin and San Mateo Counties. The California Medical Association's Council has endorsed the Bay Area survey in which more than 100 hospitals and 7,000 physicians will participate.

As contrasted with earlier national studies which were limited to demographic variables, the Third National Survey will produce a detailed analysis of cancer incidence rates, with several ad hoc reports on special problems. It is expected to provide the most extensive, comprehensive and accurate body of data ever collected on cancer and it will be an important data measure for years to come.

Data from earlier cancer surveys are out-of-date, since patterns of cancer have changed dramatically with the times. "Trends in Cancer Mortality, California, 1910-1965," issued by the State Health Department's California Tumor Registry shows that the lung cancer mortality rate for males has increased from three per 100,000 in 1920 to 42 in 1965. On the other hand, stomach cancer mortality for men has decreased in one generation, from 38 per 100,000 in 1930 to ten in 1965.

The most striking change in age-adjusted cancer death rates for women is the decrease in mortality from cancer of the uterus, from 34 per 100,000 in 1920 to 11 in 1965. The mortality rate from cancer of the stomach for women also has decreased, from 26 per 100,000 in 1930 to six in 1965. Although lung-cancer mortality in women is only one-fifth that of the male rate, the rate of increase in lung cancer mortality for women was twice that of men from 1960 to 1965, namely from six to eight per 100,000 women compared with 36 to 42 per 100,000 men.

The Bay Area Cancer Survey will be carried out by the California Tumor Registry (CTR), a central registry of 57 California hospitals, which obtains abstracts of 20,000 new cancer cases a year. This includes about one-third of newly-diagnosed cancer cases in California annually and all cases occurring in Alameda County. The CTR now has more than 300,000 cases on file and follow-up of patients is 96 percent complete.

CTR data on cancer mortality, morbidity and survival in California are useful in the planning of cancer programs throughout the state under the California Regional Medical Programs for heart disease, cancer and stroke, established by PL 89-239. A 1968 CTR publication, "Cancer Mortality, Morbidity and Survival in California," for example, provides data pertaining to the whole state and to the eight areas into which California is subdivided, each of which centers on a medical school.

The report forecasts new cancer cases by primary site and age expected in the various geographic areas, based on incidence rates generated by the Alameda County Cancer Registry, a unit of the CTR. Expected numbers of new cases for California, the regional areas and their component counties were computed by applying age-sex-site specific incidence rates for Alameda County for 1950-64 to the estimated age-sex specific populations of each county for 1967.

Data such as these are indispensable in planning for provision of medical and other services to cancer patients and their families. It is essential to predict, for instance, what kinds of cancer will occur in each sex and at what age; what kind of treatment will be required; where should appropriate treatment facilities be located for most efficient management; how many man-years and woman-years of productivity will be lost and how will families and communities bear the costs.

Success of the cancer survey will largely depend on cooperative efforts of the medical, hospital and health community, and data acquired from the study will make possible better treatment and control of cancer throughout California in the years to come.

HYPERTHERMIA DURING ANESTHESIA IN CHILDREN

"Monitoring [during anesthesia] is probably more important in children than in adults because it's sometimes more difficult to keep track of what the cardiovascular-respiratory systems are doing. A precordial or esophageal stethoscope is a *sine qua non.* In this day and age, if one wants to be sure that he is not going to overdose the patient or . . . get him into difficulty, monitoring the body temperature is of considerable importance. One can get into considerable difficulty in the newborn and the infant with a hypothermia which can develop inadvertently during the course of anesthesia. This is particularly likely to occur in air-conditioned operating rooms. In older children, one has to be aware of the possibility that occasionally they may develop a rapid, fulminant type of hyperthermia for no apparent reason. We have collected 68 patients who developed hyperthermia in this way; and of the 68, 90 per cent failed to recover. . . . There are now a number of cases . . . in the literature where patients have developed a fulminant hyperthermia and have been difficult to resuscitate. Most of the time, the difficulty in resuscitation occurred because hyperthermia was not recognized early enough. These people were not monitored with a body temperature monitor. The first thing . . . noted was that the patient's skin was hot or that the carbon dioxide absorber was hot. When body temperature was taken, it was in excess of 108 or 109 degrees Fahrenheit; and the irreversible process had begun. So if one wants to nip this in the bud . . . , the important thing is to monitor body temperature; this will give some useful information about the degree of metabolism of the patient from moment to moment."

—C. R. Stephen, M.D., Dallas

Extracted from *Audio-Digest Anesthesiology,* Vol. 10, No. 21, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

EDUCATION NOTICES

Meetings and Courses

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of the dates of continuing education programs and the meetings of various medical organizations in California is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102; or phone: (415) 776-9400, extension 241.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts
for Postgraduate Course Information

CMA:	**California Medical Association** For information contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. (415) 776-9400, ext. 241.
LLU:	**Loma Linda University** For information contact: John E. Peterson, M.D., Associate Dean for Research Affairs, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.
PMC:	**Pacific Medical Center** For information contact: Arthur Selzer, M.D., Chairman, Education Committee, Pacific Medical Center, Clay and Webster Streets, San Francisco 94115. (415) 931-8000.
STAN:	**Stanford University** For information contact: Thomas A. Gonda, M.D., Associate Dean, Stanford University School of Medicine, 300 Pasteur Drive, Palo Alto 94304. (415) 321-1200, ext. 5940.
UCD:	**University of California, Davis** For information contact: Charles J. Tupper, M.D., Dean, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0333.
UCI:	**University of California — California College of Medicine, Irvine** For information contact: Robert Combs, M.D., Associate Dean, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5221.
UCLA:	**University of California, Los Angeles** For information contact: Donald Brayton, M.D., Associate Dean and Head, Continuing Education in Medicine and the Health Sciences, 15-39 Rehabilitation Center, UCLA Center for the Health Sciences, Los Angeles 90024. (213) 825-6514.
UCSD:	**University of California, San Diego** For information contact: Clifford Grobstein, Ph.D., Dean, University of California, San Diego, School of Medicine, La Jolla 92038. (714) 453-2000.
UCSF:	**University of California, San Francisco** For information contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, Health Sciences, University of California Medical Center, San Francisco 94122. (415) 666-1692.
USC:	**University of Southern California** For information contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 225-1511, ext. 203.

MARCH

March 1-2—**NIMH Program.** UCSF at Herrick Memorial Hospital, Oakland. Saturday-Sunday.

March 1-2—**Psychiatry for General Practitioners,** UCSF at Mendocino State Hospital, Talmage. Saturday-Sunday.

March 1-2—**Computers—Horizons in Biology.** UCSF. Saturday-Sunday.

March 2-5—**Controversial Areas in Gastroenterology.** UCLA in Palm Springs. Sunday-Wednesday.

March 3-5—**Rehabilitation of Spinal Disorders.** American Academy of Orthopaedic Surgeons in Anaheim. Monday-Wednesday. 21 hours. Contact: Vernon L. Nickel, M.D., 7847 East Florence, Downey 90240.

March 4-8—**Diagnostic Radiology.** UCSF. Tuesday-Saturday. $30/day; $125, entire course.

March 4 - May 20—**Psychiatric Principles in Medical Practice.** USC Division of Postgraduate Psychiatry at Santa Clara Valley Medical Center, San Jose. Tuesdays. $35. 24 hours. Contact: Ronald A. Markman, M.D., Assistant Director, Division of Postgraduate Psychiatry, USC. (213) 225-1211, extension 336.

March 5 - May 21—**Psychiatric Principles in Medical Practice.** USC Postgraduate Psychiatry Division at Upland-Ontario. Wednesdays. $35. 24 hours. Contact: Ronald A. Markman, M.D., Assistant Director, Postgraduate Psychiatry Division, USC. (213) 225-1511, extension 336.

March 5-June 11—**Nuclear Medicine.** UCSF. Wednesdays.

March 6-7 — **WEST COAST COUNTIES — Regional Postgraduate Institute. California Medical Association in cooperation with Stanford and West Coast Counties Medical Societies.** Hyatt House, Monterey. Thursday-Saturday. 12 hours. $20. Contact: CMA.

March 6-8—**Nuclear Medicine.** UCSF. Thursday-Saturday.

March 7-8 — **Clinical Neurology: Recent Advances.** UCSF. Friday-Saturday.

March 7-12—**American Association of Pathologists and Bacteriologists.** Hilton Hotel, San Francisco. Friday-Wednesday. Contact: J. L. Orbison, Executive Secretary, American Association of Pathologists and Bacteriologists, University of Rochester, Rochester, New York 14620.

March 8—**Auscultation of the Heart.** PMC. Saturday.

March 8-9—**Children's Hospital Program II.** UCSF at Children's Hospital and Adult Medical Center, San Francisco. Saturday-Sunday.

March 9-11—**Videotape Self Observation.** UCLA in Palm Springs. Sunday-Tuesday.

March 10-21 — **Workshop in Mental Retardation.** UCLA. 10 days.

March 11-15—**Pathologic Physiology and Anatomy of the Platelet.** International Academy of Pathology at the Hilton Hotel, San Francisco. Tuesday-Saturday. Contact: F. K. Mostofi, M.D., Office of Secretary-Treasurer, Armed Forces Institute of Pathology, Washington, D.C. 20305.

March 11-15—**Diagnostic Radiology.** UCSF. Tuesday-Saturday.

March 14-15—**Medical Aspects of Well Being—Death and Dying.** UCSF. Friday-Saturday.

March 15—**Cervical Spondylosis.** PMC. Saturday.

March 15-16—**Psychiatric Program.** UCSF at Napa State Hospital, Imola. Saturday-Sunday.

March 15-16—**Techniques of Surgery of the Shoulder.** UCLA. Saturday-Sunday.

March 15-19 — **CALIFORNIA MEDICAL ASSOCIATION — Annual Scientific Assembly.** Ambassador Hotel, Los Angeles. Saturday-Wednesday. Contact: CMA.

March 19—**A Psychiatrist in Chinatown.** Agnews State Hospital, San Jose. Wednesday. Contact: J. Elizabeth Jeffress, M.D., Chief of Professional Education, Agnews State Hospital, San Jose 95114.

March 19—**San Francisco Neurosurgical Society.** Oak Knoll Naval Hospital. Wednesday evening, 6 p.m. Contact: Burton L. Wise, M.D., Room U-120, UC Medical Center, San Francisco 94122. (415) 666-1677.

March 21-23 — **Children with Learning Disorders.** UCSF. Friday-Sunday.

March 21-23—**New Concepts in the Diagnosis and Management of Pump and Electrical Failure of the Heart.** Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: William D. Nelligan, Executive Director, American College of Cardiology, 9650 Rockville Pike, Rockville, Maryland 20014.

March 22—**American Society of Clinical Oncology.** Hilton Hotel, San Francisco. Saturday. Contact: Mary E. Sears, M.D., Treasurer, American Society of Clinical Oncology, M. D. Anderson Hospital, Houston, Texas 77025.

March 22-23—**Postgraduate Assembly in Anesthesiology.** Statler Hilton Hotel, Los Angeles. Saturday-Sunday. Contact: David D. Cohen, M.D., Chairman, Postgraduate Assembly, Los Angeles County Society of Anesthesiologists, 18025 Parthenia Street, Northridge.

March 23-25 — **American Association for Cancer Research.** San Francisco. Sunday-Tuesday.

March 24-28 — **The Clinical Evaluation of Children with Learning Disorders.** UCSF. Monday-Friday. $100.

March 26-27—**Spring Symposium for Physicians Practicing General Medicine.** Statler Hilton Hotel, Los Angeles. Wednesday-Thursday. Contact: Los Angeles County Heart Association, 2405 West Eighth Street, Los Angeles 90057. (213) 385-4231.

March 26-27 — **Coronary Care and Rhythm Disturbances.** USC at Statler Hilton Hotel, Los Angeles. Wednesday-Thursday.

March 27-29—**Uveitis.** UCSF. Thursday-Saturday.

March 28—**Physicians' Symposium on Cardiovascular Diseases.** Hacienda Hotel, Fresno. Friday. Contact: Frances J. Cuthbertson, Executive Director, Central Valley Heart Association, 1759 Fulton Street, Fresno.

March 28-29—**Proctology.** UCSF. Friday-Saturday.

March 29—**Diseases of the Mouth.** UCLA. Saturday.

March 29 — **Clinical Conference in Ophthalmology.** PMC. Saturday.

March 29-30 — **Transcultural Psychiatry — Mexican-Americans.** UCSF at Agnews State Hospital, San Jose. Saturday-Sunday.

March 31-April 2—**American Association for Thoracic Surgery.** Fairmont Hotel, San Francisco. Monday-Wednesday. Contact: Thomas B. Ferguson, M.D., Executive Secretary, Suite 311, 7730 Carondelet Avenue, St. Louis, Missouri 63110.

APRIL

April 2—**Office Dermatology.** PMC. Wednesday.

April 2—**Clinical Uses of Isotopes.** PMC. Wednesday.

April 2 - June 4—**Group Methods.** UCSF at VA Hospital, San Francisco. Wednesdays.

April 5-6—**Pediatric Allergy.** PMC. Saturday-Sunday.

April 7-16 — **Cardiology for the Consultant.** Rancho Santa Fe Inn, San Diego. Two weeks. Contact: William D. Nelligan, Executive Director, American College of Cardiology, 9650 Rockville Pike, Rockville, Maryland 20014.

April 8-9—**American Association of Planned Parenthood Physicians.** St. Francis Hotel, San Francisco. Tuesday-Wednesday. Contact: Planned Parenthood, World Population, 515 Madison Avenue, New York 10022.

April 10-11—**General Surgery.** UCSF. Thursday-Friday.

April 10-12—**Current Concepts and Practice of Obstetrical Anesthesia.** UCSF. Thursday-Saturday. $75.

April 10-12 — **Western Electroencephalography Society.** Anaheim. Thursday-Saturday. Contact: E. E. Shev, M.D., 516 Sutter Street, Suite 812, San Francisco 94102.

April 11-12 — **Annual Symposium on Cardiovascular Diseases.** Sacramento-Yolo-Sierra Heart Association at Sacramento Inn, Sacramento. Friday-Saturday. Contact: Malcolm M. McHenry, M.D., Cardiopulmonary Laboratory, Sutter Memorial Hospital, 52nd and F Streets, Sacramento 95819. (916) 452-3271, extension 479.

April 11-12—**Vascular Surgery.** USC at Statler Hilton Hotel, Los Angeles. Friday-Saturday.

April 12—**Medical Emergencies.** UCLA. Saturday.

April 12-13 — **Postural Problems in Relation to the Foot.** UCSF. Saturday-Sunday.

April 12-13—**Psychiatry Program.** UCSF at Stockton State Hospital. Saturday-Sunday.

April 12-13—**Heart Conference.** RMP Area VI at Holiday Inn, Palm Springs. Saturday-Sunday. $10. Contact: John E. Peterson, M.D., Associate Dean for Research Affairs, Loma Linda University School of Medicine, Loma Linda 92354.

April 13—**Obstetrical Emergencies.** UCLA. Sunday.

April 13-17—**Pacific Coast Oto-Ophthalmological Society.** Hilton Hotel, San Francisco. Sunday-Thursday. Contact: Francis A. Sooy, M.D., Secretary-Treasurer, Department of Otolaryngology, UC Medical Center, San Francisco 94122.

April 16—**Working with the Chinese in San Francisco.** Agnews State Hospital, San Jose. Wednesday. Contact: J. Elizabeth Jeffress, M.D., Chief of Professional Education, Agnews State Hospital, San Jose 95114.

April 17-19—**Advances in Endocrinology and Metabolism.** UCSF. Thursday-Saturday.

April 17-18 — **Annual Meeting, California Thoracic Society.** El Cortez Hotel, San Diego. Thursday-Friday. Contact: William F. Roberts, Director, Public Relations Division, TB and Health Association of California, 424 Pendleton Way, Oakland 94621. (415) 636-1756.

April 18—**Neurological Evaluation.** PMC. Friday.

April 18 — **Spring Symposium in Heart Disease.** Orange. Friday. Contact: Janice Ayres, Orange County Heart Association, 1043 West 8th Street, Santa Ana 92703.

April 18-19—**The Stroke Symposium.** Alameda and Contra Costa County Heart Associations at Holiday Inn, Concord. Friday-Saturday. $25. Contact: Loyse C. Casebolt, Executive Director, Contra Costa County Heart Association, P.O. Box 212, Walnut Creek 94596. (415) 935-1060.

April 26-27—**Comparative Oncology.** UCSF. Saturday-Sunday.

April 27-29—**American Society of Maxillofacial Surgeons.** Fairmont Hotel, San Francisco. Sunday-Tuesday. Contact: Dicran Goulian, Jr., M.D., Secretary-Treasurer, 116 East 68th Street, New York 10021.

April 30 - May 3 — **American Association of Plastic Surgeons.** Fairmont Hotel, San Francisco. Wednesday-Saturday. Contact: Clarence W. Monroe, M.D., Secretary, 715 Lake Street, Oak Park, Illinois 60301.

MAY

May 2-3—**SAN JOAQUIN VALLEY COUNTIES—Regional Postgraduate Institute.** Sponsored by CMA, University of California, Irvine and San Joaquin Valley Counties Medical Societies. Friday-Saturday. 14 hours. $20. Contact: CMA.

May 2-4—**Northern California Chapter, Western Orthopedic Association.** Del Monte Lodge, Pebble Beach. Friday-Sunday. Contact: Mrs. Ida Ruth Haggerty, Executive Secretary, 3901 Ardley Avenue, Oakland 94602. (415) 533-6790.

May 3-4—**Inhalation Therapy.** UCLA. Saturday-Sunday.

May 3-4, 17-18—**Intermediate Methods in Family Therapy.** UCSF in Modesto. Two weekends.

May 5-8—**Aerospace Medical Association.** Hilton Hotel, San Francisco. Monday-Thursday. Contact: William J. Kennard, M.D., Executive Vice President, Washington National Airport, Washington, D.C. 20001.

May 5-8—**Civil Aviation Medical Association.** Hilton Hotel, San Francisco. Monday-Thursday. Contact: Charles K. Holbrook, M.D., Secretary-Treasurer, 9901 Diamond Drive, St. Louis 63137.

May 7-9—**American Association of Genitourinary Surgeons.** Del Monte Lodge, Pebble Beach. Wednesday-Friday. Contact: Harry M. Spence, M.D., Executive Secretary, 4105 Live Oak Street, Dallas 75221.

May 8—**Pediatrics Lecture.** Sponsored by Los Angeles Pediatrics Society in Los Angeles. Thursday. Contact: Mrs. Eve Black, Executive Secretary, P.O. Box 2022, Inglewood 90305.

May 8-10—**Advances in Pediatrics.** UCSF. Thursday-Saturday.

May 8-10—**Association of University Radiologists.** UC Medical Center, San Francisco. Thursday-Saturday. Contact: Harry Z. Mellins, M.D., Department of Radiology, State University of New York, Brooklyn 10021.

May 9-10—**REDWOOD REGIONAL CONFERENCE.** Sponsored by CMA, UCLA and North Coast Counties Medical Societies at Konocti Harbor Inn, Clear Lake. Friday-Saturday. 14 hours. $20. Contact: CMA.

May 9-11—**Annual Meeting, San Francisco Neurosurgical Society.** Del Monte Lodge, Pebble Beach. Friday-Sunday. Contact: Burton L. Wise, M.D., Room U-120, UC Medical Center, San Francisco 94122. (415) 666-1677.

May 9-11—**Principles of Cardiopulmonary Intensive Care.** PMC. Friday-Sunday.

May 10-11—**Love, Sex, Marriage.** UCSF at Mendocino State Hospital, Talmage. Saturday-Sunday.

May 12-15—**American Urological Association.** Hilton Hotel, San Francisco. Monday-Thursday. Contact: William P. Didusch, Executive Secretary, 1120 North Charles Street, Baltimore 20201.

May 12-17—**American Association on Mental Deficiency.** Sheraton-Palace Hotel, San Francisco. Monday-Saturday. Contact: John J. Noone, Ed.D., Executive Secretary, 5201 Connecticut Avenue, N.W., Washington, D.C. 20015.

May 15-17—**Ear, Nose, Throat.** UCSF. Thursday-Saturday.

May 17—**Application of Casts, Splints and Bandages.** UCLA. Saturday.

May 17—**Annual Seminar and Barbecue.** General Hospital of Ventura County. Saturday. Contact: Gerald K. Ridge, M.D., 3291 Loma Vista Road, Ventura.

May 21—**East Meets West.** Agnews State Hospital, San Jose. Wednesday. Contact: J. Elizabeth Jeffress, M.D., Chief of Professional Education, Agnews State Hospital, San Jose 95114.

May 23—**What's New in Medicine (UC Alumni Day).** San Francisco. Friday. Contact: UCSF.

May 23-25—**Arthritis Program.** UCSF. Friday-Sunday.

May 23-25—**Frontiers in Medicine.** UCSF and Humboldt-Del Norte Medical Society in Eureka. Friday-Sunday. Contact: UCSF.

May 24-25—**Psychiatry Program.** UCSF in Sacramento. Saturday-Sunday.

BOOK REVIEWS

California Medicine does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

HANDBOOK OF PEDIATRIC MEDICAL EMERGENCIES — Fourth Edition — Charles Varga, M.D., Associate Clinical Professor of Pediatrics, University of Oregon Medical School, Senior Attending Pediatrician, The Permanente Clinic and Bess Kaiser Hospital, Portland, Oregon. The C. V. Mosby Co., 3207 Washington Boulevard, St. Louis, Mo. (63103), 1968. 694 pages, with 120 illustrations, $19.75.

This is the fourth and much improved edition of this volume. It is edited by Dr. Varga alone due to the recent death of Dr. De Sanctis who was formerly co-editor. It is so extensively revised and enlarged, by 248 pages, as to construct a new book rather than a revision. Of 14 major contributors ten are new. This book fulfills the promise of its title very well indeed. It should prove adequate in information and detail for almost all pediatric medical emergency situations. The section on poisons is particularly good and alone might justify the purchase of the book.

William C. Deamer, M.D.

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PEDIATRICS — 14th Edition — Henry L. Barnett, M.D., Professor and Chairman, Department of Pediatrics, Albert Einstein College of Medicine, Yeshiva University; Director, Pediatric Service, Bronx Municipal Hospital Center, Bronx, New York. With the collaboration of Arnold H. Einhorn, M.D., Associate Professor of Pediatrics, Albert Einstein College of Medicine, Yeshiva University; Director, Pediatric Service, Lincoln Hospital, Bronx, New York. Appleton-Century-Crofts, Division of Meredith Corporation, 440 Park Avenue South, New York, N.Y. (10016), 1968. 1847 pages, $24.50.

This large and comprehensive new textbook of pediatrics reflects the combined efforts of Dr. Barnett, his collaborative editor, Dr. Einhorn, 18 associate editors and over 100 other contributors. In keeping with the senior editor's belief that the practicing pediatrician will become increasingly "a specialist in general pediatrics" and that many of his present functions will in the future be delegated to nurses and paramedical personnel, considerable space is assigned to mechanisms of disease and applications of the basic sciences. This is not to say however that clinical and practical considerations receive secondary attention; the discussions of such threadbare topics as colic, enuresis and breast feeding are models of succinctness and common sense. Therapeutic measures of proven value are clearly distinguished from those whose value is less certain. The importance of the book as a reference text is enhanced by lengthy and well-organized lists of references at the end of each section.

The format of the book is conventional with early chapters devoted to growth and development, general problems of child health and perinatal pediatrics. Thereafter children's diseases are considered according to the principal organ system involved. One might question some of the organization of the material; for example the trisomy syndromes are discussed under mental retardation in the section on the nervous system rather than in the section on genetics. The detailed discussion of cell ultrastructure in the liver section might lead the unwary to believe that such cell organization is unique to the liver cell. The illustrations are adequate, but the color plates, which are of small size and are grouped together at the beginning of the book, are somewhat disappointing. Larger plates of a few carefully selected lesions would have been more informative. The charts and figures are valuable, although some of them require careful study because of the complex nature of the material presented.

The emphasis on mechanisms of disease and a basic science approach makes this a particularly valuable book for medical students, residents and for those preparing for board examination. Certainly no teaching hospital library should be without it. For the practitioner, the book is unique among available texts in providing a blend of practical and basic science material presented in a fresh and lucid manner. It should be required reading for all physicians who wish to keep up with the rapidly changing field of modern pediatrics.

Paul F. Wehrle, M.D.

California
Medicine

Contrast Media

The Present Status of Water-Soluble Iodine-Containing Material in the Examination of Acute Abdominal Disease

ALEXANDER R. MARGULIS, M.D., *San Francisco*

MR. CHAIRMAN, MRS. GARLAND, *Members of the Society and Guests: I am deeply grateful to the California Radiological Society for the honor of inviting me to deliver the Second L. H. Garland Memorial Lecture. The opportunity to pay homage and tribute to a great man, to an irreplaceable leader of radiology, is indeed a great privilege. I am also indebted to fate for the good fortune of having been one of Harry Garland's friends and coworkers. The sadness we all feel because he no longer is with us does not diminish, but grows constantly. As our problems increase in volume and complexity, we miss his sage advice and leadership. With his clear, logical mind, he crystallized issues as few others could. He possessed the courage to face unpleasant tasks and to defend that which he believed was right. His wit and ability of expressiveness, his charm and elegance of conduct, are qualities not matched by many others. Our gatherings are less lively, more conventional and more rigid without the spark of his bright presence.*

Harry Garland was born in Dublin, Ireland, in 1903. He obtained his medical degree there in 1924 from the University College. He came to San Francisco for a visit and stayed here, enriching the life of all who were so fortunate as to have contact with him. He trained in radiology at Stanford University with Doctors Chamberlain and Newell and remained there on the clinical faculty until 1960. By that time he had attained the rank of full clinical professor. It was in 1960 that he became Clinical Professor of Radiology at the University of California. Most of his teaching efforts were directed toward creating and nurturing the teaching of radiology at the San Francisco General Hospital from 1929 until his death. He was an indefatigable teacher, a virtuoso unexcelled in his approach and ability to maintain unfailing interest of students and residents. His conferences at San Francisco General Hospital, at the universities at which he taught, and at national conventions are unforgettable.

Harry Garland was a leader in the clinical investigation of radiologic diagnosis and his contributions were numerous and significant. His work on the diagnosis of chest diseases, on the reliability of roentgenographic interpretation, and on the growth of metastatic nodularities in the lung are classics, not only in content but also in medical writing.

In public life, Harry was a leader, a courageous fighter for his beliefs and a most distinguished representative of radiology. The offices he held are too numerous to list. The honors he received and richly deserved are equal to those of a dozen men of achievement. The one that afforded him greatest pleasure was an honorary M.D. degree bestowed on him by his alma mater, the University of Dublin. He was one of the founders and was the guiding light of the California Radiological Society until his death. Professionally, he was highly respected by his patients and colleagues.

The L. H. Garland Memorial Lecture, presented at the 97th Annual Meeting of the California Medical Association, San Francisco, March 23 to 27, 1968.

From the Department of Radiology, University of California School of Medicine, San Francisco.

Reprint requests to: Department of Radiology, University of California, San Francisco Medical Center, San Francisco 94122.

His interests besides medicine were multitudinous. He was a connoisseur of art, an epicure, and an important participant in the cultural activities of San Francisco.

Although Harry Garland spent much of his professional life in the combat of cancer, his own personal fight against this disease was unsuccessful. He succumbed as only he could—undaunted, fearless, planning, and inspiring others to the last moment.

The topic I have chosen for this lecture is "The Present Status of Water-Soluble Iodine-Containing Contrast Media in the Examination of Acute Abdominal Disease." Currently this subject is highly controversial. The media used in these examinations need to be viewed in their proper perspective. This is the sort of task that Harry liked to tackle throughout his professional life. It is in this spirit that I dedicate this lecture to the memory of L. Henry Garland.

Physicians in general and radiologists in particular are subject to fads. A new procedure, a new drug or a new contrast medium is heralded as applicable in a far wider field than is warranted. Expectations are raised and the use of the particular adjunct becomes general. The first published articles by enthusiastic investigators report results that reflect a somewhat favorable bias for the particular drug or procedure. Reports of subsequent failures soon follow, particularly when the new measure was applied at the wrong indication. Disappointment leads to abandonment. After a few years, new attempts shed light on the proper indications. If the measure is worthwhile, its proper place and function will be established, albeit these will be much more limited than promised originally.

This same pattern of enthusiasm, disappointment and designation, followed the introduction of water-soluble contrast media in the examination of acute conditions of the abdomen. Barium sulfate is known to become inspissated in the colon proximal to an obstruction of the large bowel. It may convert a partial obstruction of this bowel to complete obstruction.[1] In the minds of many surgeons, this sequence became confused with that following administration of barium when the small bowel was obstructed. Many believed, erroneously, that similar inspissation might occur proximal to a small bowel obstruction. Based on hearsay, this postulate, even today, results in the reluctance of many surgeons and internists to use barium sulfate in patients with small bowel obstruction. As early as 1954, Frimann-Dahl[1] advocated the oral administration of barium sulfate for study of an acute obstruction of the small bowel. Such administration was particularly recommended when a barium enema examination had excluded obstruction of the large bowel. In animals with experimentally produced small bowel obstruction, Donato, Mayo, and Barr[2] showed that barium sulfate suspension may be used without danger of inspissation.

Barium sulfate became the contrast medium of choice for the examination of the small bowel when mechanical obstruction was suspected. The patient drank the suspension or it was injected through a long tube, the tip of which was located at or near the site of the mechanical obstruction. Slow movement, however, of the ingested barium sulfate through the small bowel soon became apparent in patients afflicted with both adynamic and mechanical ileus. Barium was clearly contraindicated in patients in whom the viability of bowel was in question or in whom perforation was suspected.

In 1955, Canada[3] introduced the concept of using a water-soluble contrast medium that contained iodine for the examination of the gastrointestinal tract. A number of other investigators[4-9] followed suit. Davis, Huang, and Pirkey[4] were aware that because of hypertonicity the water-soluble contrast media could act as laxatives of the saline type. They reported the development of diarrhea in normal subjects who had ingested 50 ml of 70 per cent Urokon.® By employing Hypaque® and Renografin®, Epstein[5] was able to demonstrate the location of intestinal loops as well as partial and complete small bowel obstruction. Other investigators[5,6,8] also demonstrated that the water-soluble, iodine-containing contrast medium became diluted in the distal small bowel. Nelson and coworkers[10,11] and Harris, Neuhauser, and Girth[12] proved that iodinated radiopaque media in the small bowel may cause loss of fluid into the bowel lumen, aggravation of hypovolemia, and dehydration. Vest and Margulis[13] have shown the great value of a water-soluble, iodine-containing contrast medium in differentiating postoperative adynamic ileus from mechanical obstruction.

What, then, is the place of water-soluble iodinated contrast media? Should they be used ever? If so, what are their indications, advantages, and disadvantages?

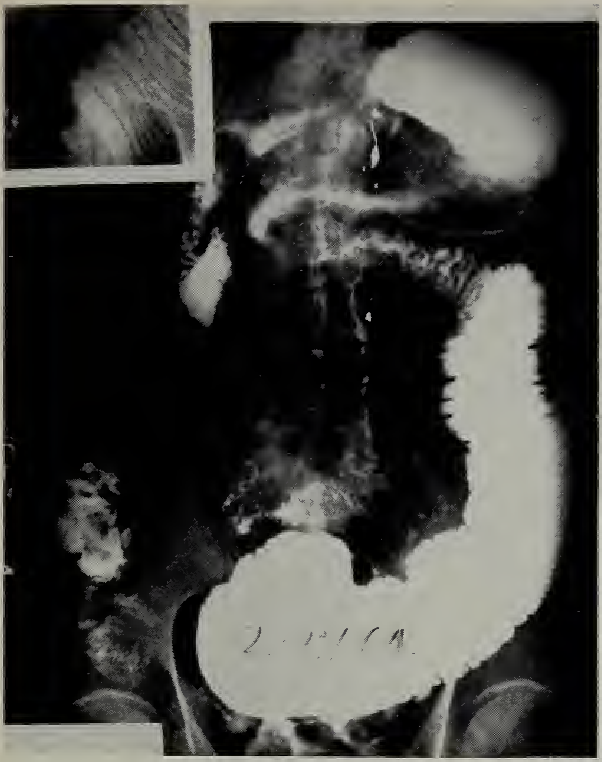

Figure 1.—Four-hour roentgenogram following administration of barium in a patient with partial mechanical small-bowel obstruction from carcinoma of the distal jejunum. *Inset:* Compression spot-film showing the characteristic diagnostic details at the site of obstruction.

Advantages of Barium Sulfate

Barium sulfate produces uniformly good contrast in the gastrointestinal tract. It is suspended in water and, therefore, is not hypertonic. It is usually administered with a suspending agent, allowing suspension even when fluid and mucus are met in distended small bowel loops. Because of these advantages, barium sulfate is an excellent contrast medium. It should be the medium of choice to demonstrate not only the presence of obstruction, but also its site and nature. With a fluoroscopically controlled examination, compression spot-films are obtainable to show detail at the site of obstruction (Figure 1).

Injection of barium through a long tube that has been passed will render even more consistently such detail.[14] The administration of barium to dehydrated patients is possible. When properly performed, an examination with barium sulfate results in a definitive study.

Disadvantages of Barium Sulfate

Certain disadvantages to the use of barium do exist. Because of its lack of hyperosmolarity, barium sulfate progresses slowly through an adynamic bowel. In a postoperative patient, a wait of

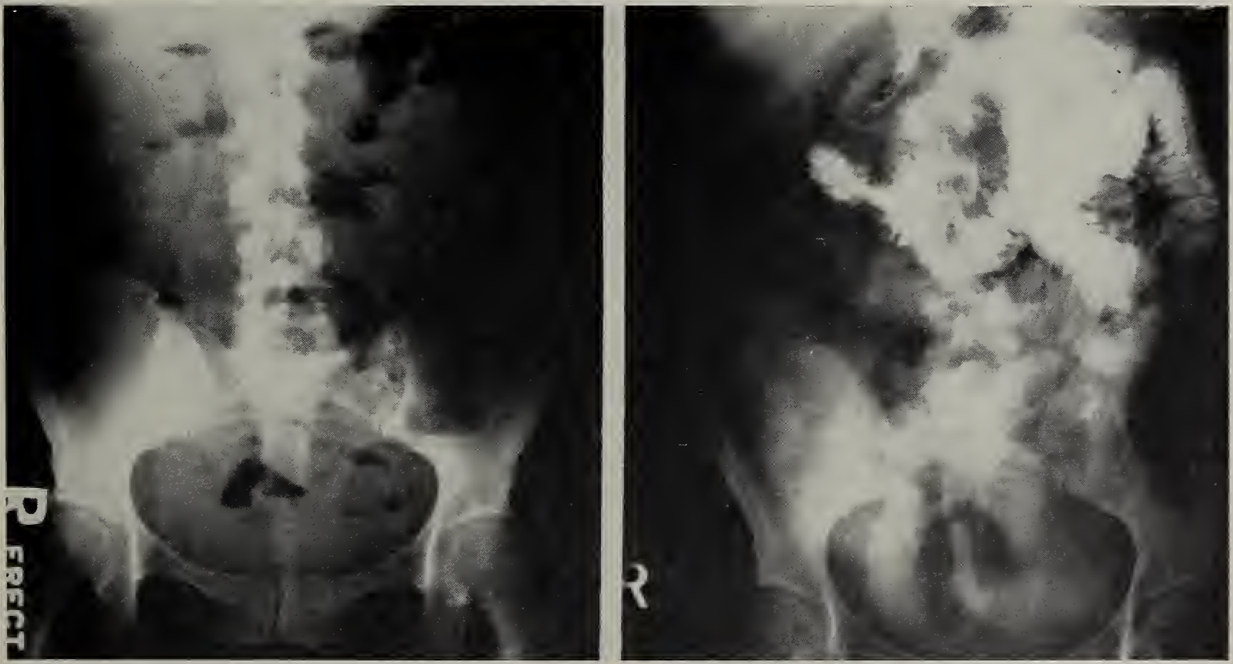

Figure 2.—*Left:* Plain roentgenogram in upright projection, interpreted as indicative of partial small-bowel obstruction in a patient with long standing hypertension and abdominal pain. *Right:* An eight-hour roentgenogram of the small bowel after administration of barium, interpreted as showing small-bowel obstruction. The patient had been receiving ganglion-blocking agents for several years. A laparotomy was performed; no obstruction was found. Roentgenograms of the small bowel with barium sulfate as the contrast agent must show the actual site of obstruction if interpretation is to be reliable.

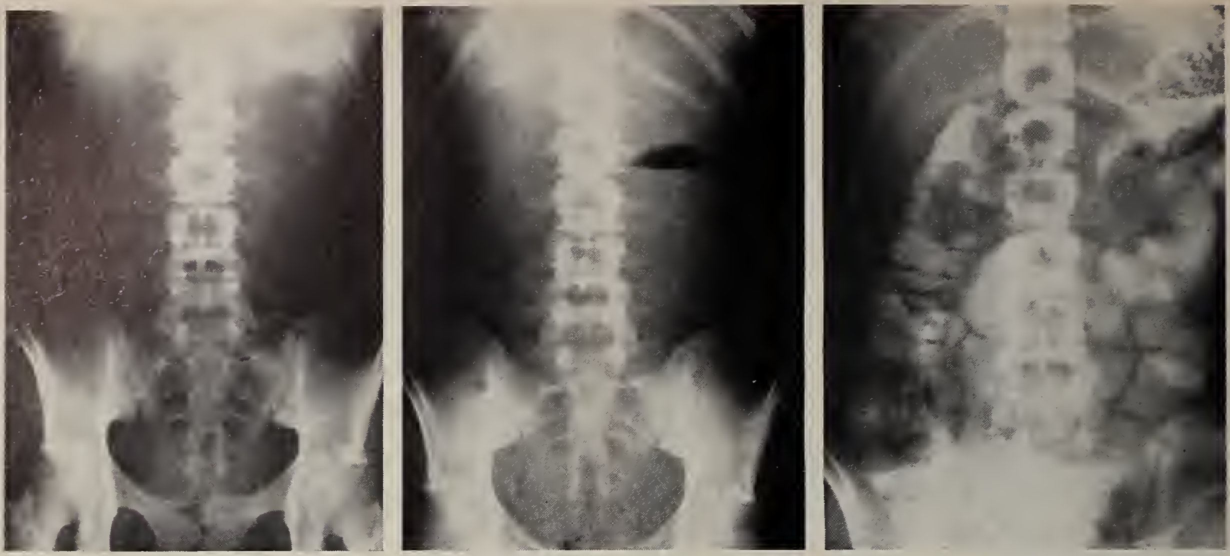

Figure 3.—*Left:* Plain supine roentgenogram of the abdomen. *Center:* Upright plain roentgenogram of the abdomen 11 days after repair of a strangulating small-bowel obstruction. Roentgenograms were interpreted as showing a postoperative mechanical small-bowel obstruction. *Right:* One and a half hours after administration of 100 ml of 40 percent Hypaque® by mouth, the contrast medium has reached the colon. There is dilatation of the jejunum with a differential in the diameter of the lumen of the jejunum compared to that of the ileum. The appearance is that of a low grade, partial obstruction of the small-bowel. The patient improved rapidly and spontaneously and was discharged a few days after this study.

24 hours may be necessary before adynamic ileus can be differentiated from mechanical small bowel obstruction. Impatience and hasty conclusions can lead to mistakes. Similarly, barium moves slowly in patients given ganglion-blocking drugs (Figure 2). In postoperative patients with complications a long tube cannot be passed without difficulty. Usually then, the radiologist is not granted the leisureliness of an examination with barium. The surgical team must often decide whether or not reoperation is necessary within a few hours. The same principle applies also in a patient with a suspected closed-loop obstruction. In such a patient, particularly if the small bowel is not viable, barium given orally moves too slowly to render the diagnosis. In instances in which a perforation follows the closed-loop obstruction, barium may actually increase the dangers. Barium is contraindicated whenever perforation is suspected. Barium crystals and the suspending agents produce an inflammatory reaction resulting in dense adhesions.[15-17]

Water-Soluble, Iodine-Containing Media

What are the contraindications and indications for the use of water-soluble, iodine-containing contrast media in the examination of acute abdominal disease? The hyperosmolarity of contrast medium of this type presents simultaneous disadvantages and advantages. Because of dilution, the roentgenographic detail becomes poorer as the contrast material progresses in the small bowel. The site of obstruction in the small bowel can almost never be identified adequately and its nature is almost never apparent. If the examination is not closely monitored with frequent roentgenograms, a partial obstruction is sometimes missed in the proximal bowel. Close attention must be given to the relative width of the loops of the small bowel. Otherwise, frequently a partial obstruction in the distal small bowel may be overlooked. Large amounts of contrast medium given to dehydrated patients may aggravate hypovolemia; shock and even death may result. This is particularly true in infants and in the aged.

Some of the advantages of this medium also depend on its hypertonicity. In postoperative patients particularly, it acts as a saline type of laxative. The transit time through the small bowel is considerably accelerated.[18] Noonan and Margulis[19] have shown that in cats the transit time of Hypaque administered orally is significantly shorter than that of barium. This was true in normal cats as well as in cats after parenteral administration of probanthine or after laparotomy involving handling of the bowel. This hypertonicity with its resulting laxative effect of iodinated, water-soluble contrast media implies even a therapeutic as well as purely diagnostic use. Not infrequently, bowel movement starts after administration of such a medium for

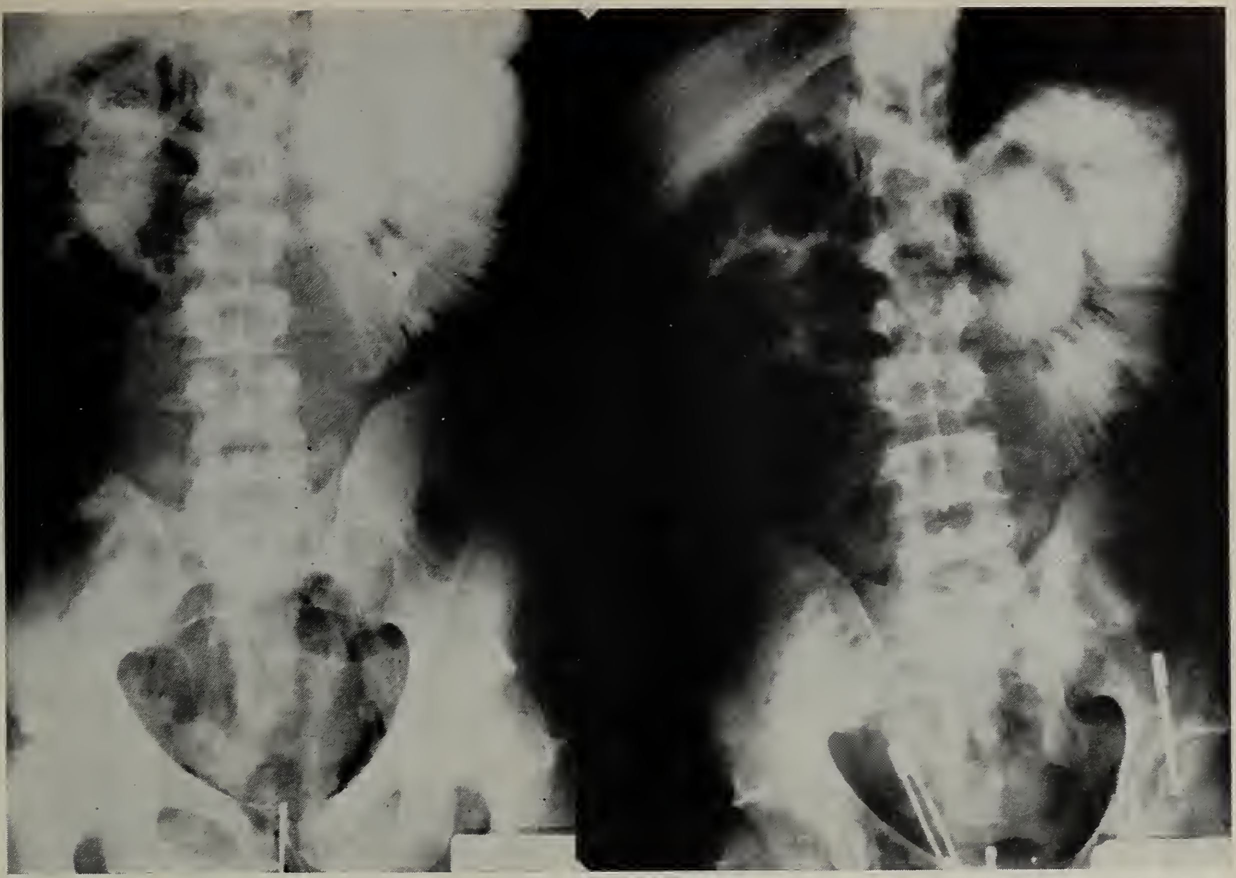

Figure 4.—Roentgenograms taken an hour and a half (left) and three and a half hours (right) after oral administration of Hypaque® in a patient with a proved closed-loop, strangulated obstruction of the jejunum occuring on the tenth postoperative day after operation on the colon. The strangulated jejunal loop was viable. The fluid-filled loop of bowel is well demonstrated against the dilated contrast medium filled jejunum and duodenum.

examination of a suspected postoperative obstruction. In some patients the postoperative, adynamic ileus with concomitant dilatation of the small bowel produces a low grade, partial obstruction of the small bowel around adhesions. The induction of peristalsis by the water-soluble, iodine-containing contrast medium reduces the obstruction by emptying the bowel and thus decreasing the dilatation and unkinking the bowel. The water-soluble, iodinated contrast medium does not reveal the exact location of an obstruction or the nature of the lesion. The surgeon is informed by the study, however, whether an obstruction or a paralytic ileus is present (Figure 3).[13]

In closed-loop, small bowel obstructions, the strangulation of blood supply for a sufficiently long time produces necrosis of the bowel. Water-soluble contrast media or barium will not then leave the stomach or duodenum.[20,21] When the closed loop of an obstructed small bowel is not necrotic, the iodinated medium progresses rapidly. The fluid-filled, obstructed loop then produces an impression on the proximal loops that contain contrast material (Figure 4).

The water-soluble medium is also indicated in severely ill patients in whom obstruction of the small bowel is suspected. These patients usually cannot tolerate a barium enema examination to rule out conclusively colonic obstruction.

The least controversial and the greatest use for these media is for suspected perforation of a viscus. The determination of its presence and location is important.[22,23] The site of perforation, whether the result of a postoperative anastomotic leak or of a perforated ulcer, can be demonstrated readily (Figure 5). The cause and the site of such lesions are not clinically obvious.

An imaginative use of water-soluble contrast media has been described by Steichen and coworkers.[24] It provides the criteria for diagnosis of intraperitoneal penetration from stab wounds or gunshot wounds of the abdomen. In the 100 patients with such wounds who were studied, Steichen injected water-soluble iodinated media and noted

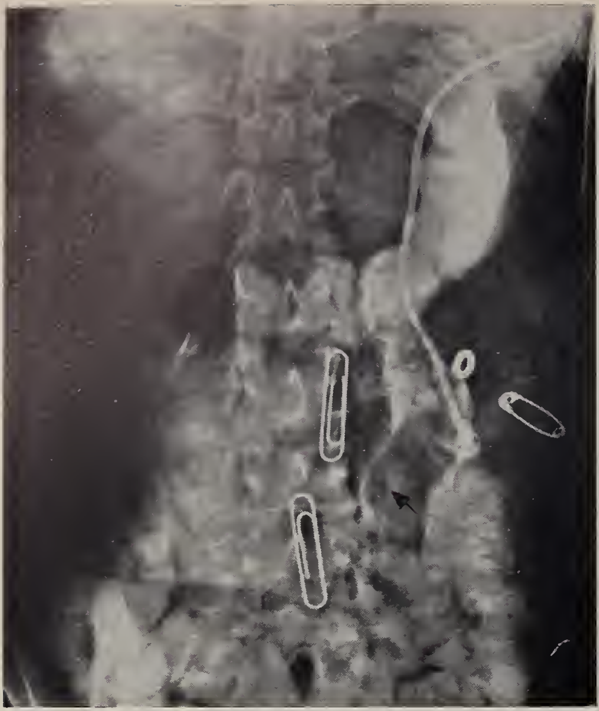

Figure 5. — Hypaque® study after total collectomy for chronic ulcerative colitis in a young woman receiving large doses of cortisone. The perforation through a jejunal ulcer (arrow) is well demonstrated.

that in 63 of the patients there was no intraperitoneal penetration. Thus, an unnecessary operation with its increased morbidity was avoided in these patients. In 36 patients demonstration of intraperitoneal penetration and determining the site permitted the operative procedure to be more precise. It appears that there could be considerable use of this technique in this application, particularly in hospitals with active emergency wards and in battlefield medicine (Figure 6).

Postoperative cutaneous fistulas, which may connect with the peritoneal cavity, also are demonstrated precisely and safely with water-soluble, iodinated contrast media. When corticosteroids have been administered for a long time before the laparotomy and must be continued after the operation, perforation of ulcers is a frequent complication. These perforations are best studied with the iodinated, water-soluble contrast media. They may be located in unusual sites and may not be suspected clinically (Figure 5).

A further indication for the use of these contrast media is in the presence of acute dilatation of the stomach in severely ill patients. Acute gastric dilatation is sometimes difficult to differentiate roentgenographically from cecal volvulus. A few drops of Hypaque or Gastrografin® administered through a nasogastric tube may solve the question without resort to barium enema, an important consideration in a situation in which the stomach may rupture at any time.

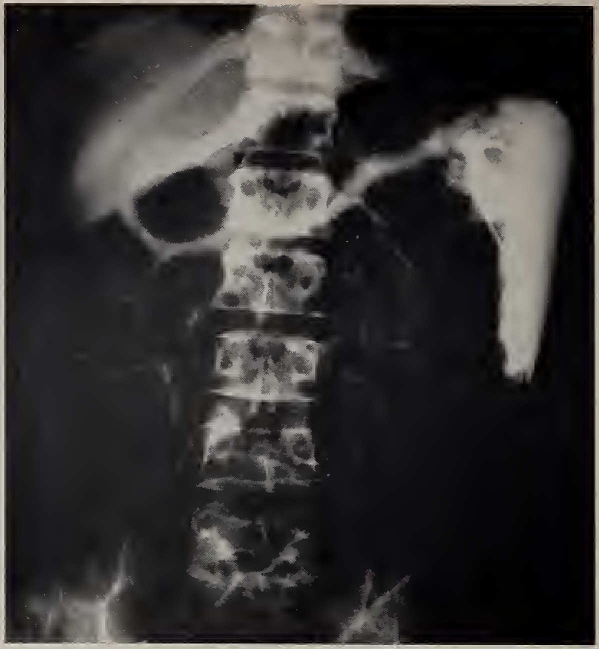

Figure 6. — Water-soluble iodinated contrast medium was injected through an abdominal stab wound. The contrast medium is extraperitoneal. No laparotomy was required.

Opacification of the Urinary Bladder

Mori and Barrett[25] described opacification of the urinary bladder that followed administration of oral contrast media in the presence of perforation. They expressed the belief that this is a valuable diagnostic sign to suggest the presence of such a perforation. The contrast medium is absorbed from the peritoneal cavity and excreted through the urinary system. However, absorption of iodinated water-soluble contrast media from the gastrointestinal tract has been apparent as well. In many adults, and even more frequently in children, it is absorbed in sufficient quantity to opacify the urinary bladder, but probably not the calyceal system. The absence of opacification of the bladder after ingestion of such media is strong evidence against a perforation. On the other hand, the demonstration of contrast media in the bladder may not mean perforation. If the calyceal system is seen, the existence of a perforation is most likely.

Conclusions

Barium sulfate still remains the medium of choice in the detection of the site of intestinal obstruction and in resolving its nature.

Water-soluble, contrast media act as radiopaque saline laxatives with all the advantages and disadvantages of hypertonic media. They provide the more general information as to the presence of adynamic ileus as against mechanical obstruction. These contrast media have been shown to move through the gastrointestinal tract more rapidly than does barium.[18,19] Barium sulfate should not be used when perforation of the bowel is suspected. Organic water-soluble iodides are indicated in this instance and in the study of knife and gunshot wounds of the abdomen. Perhaps in the future an iodinated contrast agent will be developed which will be suspended within the gastrointestinal tract and result in excellent detail. Ideally, once it is passed into the peritoneal cavity through a perforation, it should be completely absorbed. Such media are not available at present, but investigations to develop them are under way.

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Diagnosis of Congenital Heart Dise

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■ *The differential diagnosis of congenital heart disease which presents cyanosis or respiratory distress, or both, in the first two weeks of life, is difficult. Close correlation of clinical features, electrocardiogram and chest roentgenogram is most helpful. The diagnosis of congenital heart disease should lead to immediate cardiac catheterization, angiocardiography and appropriate therapy.*

DETERMINATION OF THE cause of respiratory distress or cyanosis, or both, in a newborn infant is often difficult. Distress caused by congenital heart disease is frequently hard to distinguish from that secondary to primary pulmonary disease, such as the respiratory distress syndrome, the aspiration syndrome, and the distress from diaphragmatic hernia. Since no murmur is audible in one-third of neonates with congenital heart disease, the difficulty of differentiation becomes further accentuated. Roentgenography of the chest aids greatly in eliminating many noncardiac causes of newborn distress.

The purpose of this presentation is to offer an approach to the diagnosis of the most common types of congenital heart disease associated with respiratory distress or cyanosis, or both, in the first two weeks of life. Accurate diagnosis in this age group entails careful correlation of physical findings, electrocardiogram and roentgenogram of the chest (Table 1). This correlation requires good communication between pediatrician and radiologist. The probability that the symptoms in a neonate are the result of congenital heart disease should lead to immediate cardiac catheterization and angiocardiography to define all aspects of the abnormality. Prompt diagnosis is essential to optimal management.

Careful attention to roentgenographic technique should include optimal positioning, careful coning, proper exposure factors and short exposure time. Accurate delineation of the state of the pulmonary vasculature and interstitial markings is necessary because of the importance of differentiation of these features from parenchymal abnormalities. Pulmonary edema is manifested by congested vasculature, hazy vascular margins, interstitial edema with hazy reticular pattern, Kerley's lines, thickened fissures and pleural effusion.

When the diagnosis remains uncertain after the initial studies and the infant is not so ill as to necessitate immedate cardiac catheterization and angiocardiography, serial chest roentgenograms should be obtained. In patients whose congenital heart lesions are associated with classic cardiac enlargement and increased pulmonary vasculature, the size of the heart and the vasculature may appear normal on initial examination. Pulmonary edema may not develop in the first few days of life.

The following entities are the more commonly encountered forms of heart disease associated with cyanosis, respiratory distress, or both, in the first two weeks of life.

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Dr. Bessolo is a trainee in cardiovascular radiology. Supported by NIH Training Grant I T12 HE 5824-1 from the U.S. Public Health Service.

Submitted 29 July 1968.

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the First Two Weeks of Life

Complete Transposition Of the Great Vessels

Complete transposition of the great vessels is the most common congenital heart lesion causing cyanosis in the newborn period.[1-4] As a rule, patients with transposition are cyanotic without respiratory distress during the first day of life. Symptoms of congestive heart failure begin to appear in this group of patients between two and ten days after birth. The electrocardiogram usually is consistent with right ventricular hypertrophy.

The classic roentgenographic appearance of complete transposition of the great vessels consists of a large heart with increased vascularity (Figure 1). In the first week of life this most commonly described appearance is often not seen because of the normally high neonatal pulmonary vascular resistance. Regardless of size, however, the cardiac silhouette is typical in more than 80 per cent of cases. The heart is egg-shaped with a narrow vascular pedicle (Figures 2 and 3). The base of the "egg" is the enlarged right atrium. The apex is elevated from right ventricular enlargement. The left upper heart border is convex as a result of an enlarged left ventricle. In the frontal view, the vascular pedicle appears narrow because the aorta and pulmonary artery are nearly superimposed and the course of the aorta follows a sagittal plane rather than its usual oblique course. The pulmonary vascularity is usually normal and only becomes increased after one to three weeks of life, with concomitant enlargement of the cardiac silhouette. When neonatal cyanosis is associated with the classic egg-shaped heart and narrow vascular pedicle, catheterization and angiocardiography should be performed immediately. These procedures establish the diagnosis and determine the site and functional adequacy of the communications between the systemic and pulmonary circulations (atrial septal defect (ASD), ventricular septal defect (VSD), and patent ductus arteriosus (PDA)). A Rashkind maneuver (balloon atrial septostomy) and subsequent surgical procedure may be lifesaving.[5]

Transposition of the great vessels with coarctation of the aorta is a common combination of serious congenital heart lesions in the newborn.[2] These infants are cyanotic but congestive heart failure develops at an earlier age than it does in isolated transposition. The electrocardiogram usually reveals right ventricular hypertrophy. A large heart with increased pulmonary vasculature and congestive heart failure with interstitial pulmonary edema are revealed on the roentgenogram of chest (Figure 4).

Left-sided Obstructive Lesions

Hypoplastic left heart. The hypoplastic left-heart syndrome includes hypoplasia or atresia of the aortic or mitral valve, or of both valves, and is regularly associated with a hypoplastic left ventricle. Most of the pulmonary venous return flows from the usually small left atrium to the right atrium and from there reaches the systemic circulation through the right ventricle, pulmonary artery and a large patent ductus arteriosus. This syndrome is the most common cause of congestive heart failure in the newborn period,[2,6] and its manifestations are tachypnea, signs of congestive heart failure, generalized decreased peripheral pulses and minimal cyanosis.[1,6,7] The electrocardiogram usually reveals right ventricular hypertrophy, primarily because of lack of left ventricular (posterior) forces.

The roentgenogram of the chest reveals a large heart with increased pulmonary vasculature and pulmonary edema manifested by blurring or lack of sharpness of the vascular outlines, a hazy reticular interstitial pattern and occasional pleural thickening (Figure 5). The right border of the heart may be disproportionately large (Figure 6). Usually these patients die within the first or second week of life.

Coarctation of the aorta with ventricular septal defect. Congestive heart failure in the newborn period associated with coarctation of the aorta is the result of either severe coarctation, or, more frequently, the combination of coarctation of the aorta and ventricular septal defect.[2] Elicitation of the pulse differential between the upper and lower extremities, diagnostic of coarctation of the aorta in the adult, is difficult in the newborn. A difference in the blood pressure in the upper and lower extremities, when found, however, is strongly suggestive of this disease. Although the electrocardiogram in the older child with coarctation is consistent with left ventricular hypertrophy, in the neonate it usually indicates right ventricular hypertrophy as a result of increased blood flow through the right ventricle.

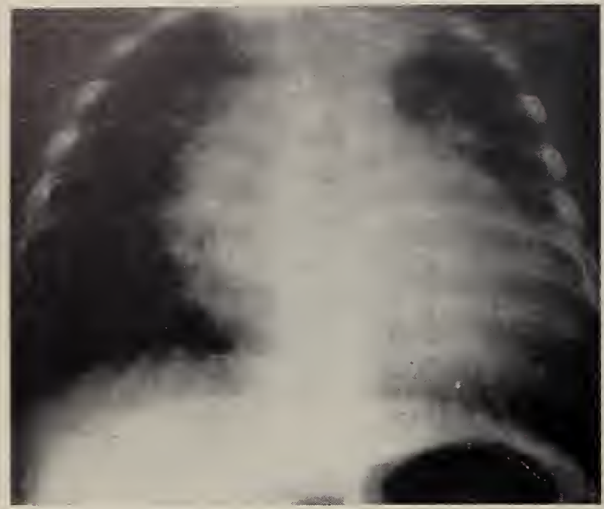

Figure 1.—Complete transposition of great vessels, atrial septal defect, and patent ductus arteriosus (necropsy) in a three-month-old male with cyanosis since birth. Electrocardiogram: Right ventricular hypertrophy. Roentgenogram: Classic enlarged egg-shaped heart, narrow vascular pedicle, and increased pulmonary vasculature.

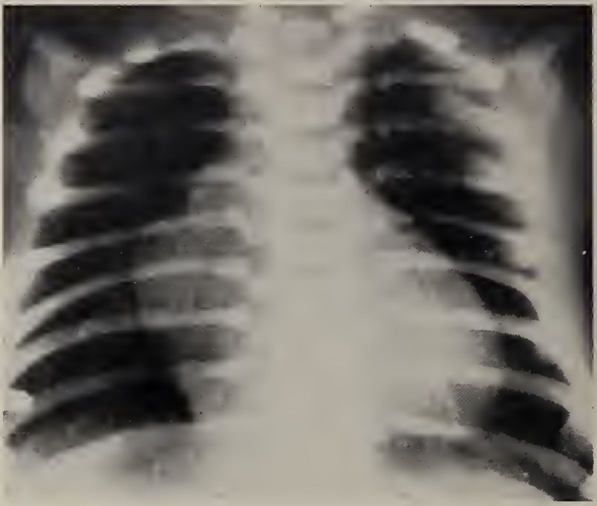

Figure 2.—Complete transposition of great vessels, atrial septal defect, and patent ductus arteriosus (angiocardiogram) in a two-day-old female who had had cyanosis without distress, since four hours of age. Electrocardiogram: Right ventricular hypertrophy. Roentgenogram: Typical egg-shaped heart, narrow vascular pedicle, and normal pulmonary vasculature.

TABLE 1.—*Differential characteristics of congenital heart disease in the newborn*

	Heart—Size and Shape	*Pulmonary Vasculature*	*Electro-cardiogram*	*Distinguishing Clinical Features*
Transposition	Egg-shaped; narrow vascular pedicle	Normal; later increased	RVH	Cyanosis in first day without distress
Hypoplastic left heart	Large	Increased with pulmonary edema	RVH. Absence of left forces	Symmetrically decreased pulses and respiratory distress.
Coarctation of aorta with VSD	Large	Increased with pulmonary edema	RVH	Decreased lower extremity blood pressure
Total anomalous pulmonary venous return below diaphragm	Normal	Pulmonary edema	Pronounced RVH	Mild cyanosis
Myocardiopathy	Large	Initially normal, later pulmonary edema	LVH (80%) with ischemia	
Peripheral A-V fistula	Large	Pulmonary edema	RVH	Bruit
Hypervolemia	Large	Pulmonary edema	Normal	Rising hematocrit
Pulmonary atresia with intact ventricular septum	Large	Decreased	Four-fifths have LVH	Cyanosis in first day
Severe pulmonic stenosis	Large	Decreased	Pronounced RVH	Mild cyanosis
Severe tetralogy of Fallot	Normal (25% right aortic arch)	Decreased	RVH	Cyanosis in first day
Tricuspid atresia	Normal	Decreased	Left axis LVH	Cyanosis in first day

RVH=right ventricular hypertrophy. VSD=ventricular septal defect. A-V=arterio-venous.

The roentgenogram of the chest reveals a large heart with increased pulmonary vasculature and signs of congestive heart failure with interstitial pulmonary edema. The left atrium is often enlarged and its size may be a helpful point in differentiating between coarctation of the aorta and hypoplastic left heart.

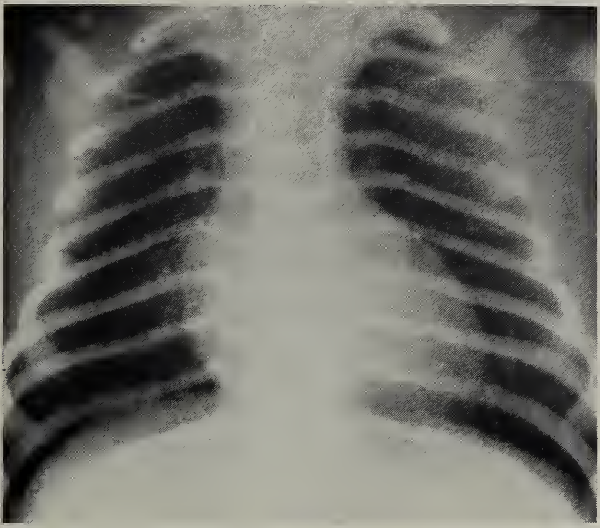

Figure 3.—Complete transposition of great vessels and atrial septal defect (necropsy) in a three-day-old male with cyanosis since birth. Congestive heart failure developed during the second day of life. Electrocardiogram: Right ventricular hypertrophy. Roentgenogram: Normal-sized, typically egg-shaped heart, narrow vascular pedicle, and normal pulmonary vasculature.

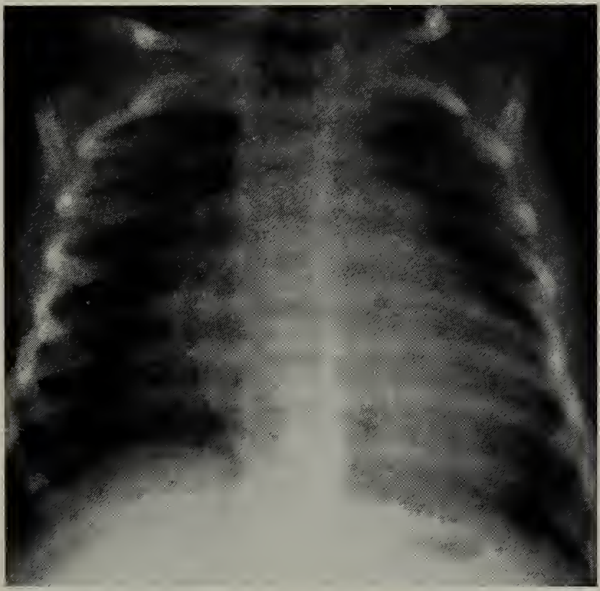

Figure 4.—Complete transposition of great vessels, preductal coarctation of aorta, atrial septal defect, ventricular septal defect and patent ductus arteriosus (necropsy) in a five-day-old female with mild cyanosis at birth, increasing tachypnea and cyanosis after two days of age. Blood pressure (flush) suggested lower pressure in legs. Electrocardiogram: Combined ventricular hypertrophy. Roentgenogram: Slight enlargement of heart with nonspecific configuration, increased pulmonary vasculature with congestive heart failure manifested by hazy vascular margins, and diffuse interstitial hazy pattern.

Total anomalous pulmonary venous return of the obstructed type, usually below the diaphragm. This type of total anomalous return below the diaphragm, because of severe obstruction to pulmonary venous flow through the liver, is associated

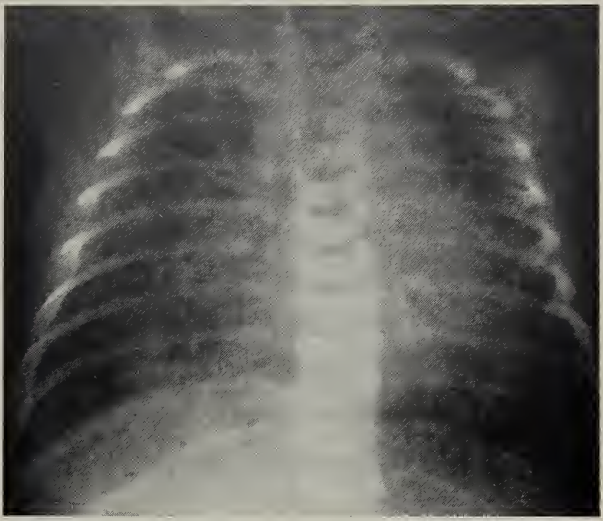

Figure 5.—Hypoplastic left heart in a one-day-old male with congestive heart failure, symmetrically decreased pulses, and dusky cyanosis. Electrocardiogram: Absent left ventricular (posterior) forces. Roentgenogram: Slight cardiomegaly, increased pulmonary vasculature with severe interstitial pulmonary edema. Necropsy: Hypoplastic left ventricle diminutive mitral valve ring and orifice, absent atrial septum and large patent ductus ateriosus.

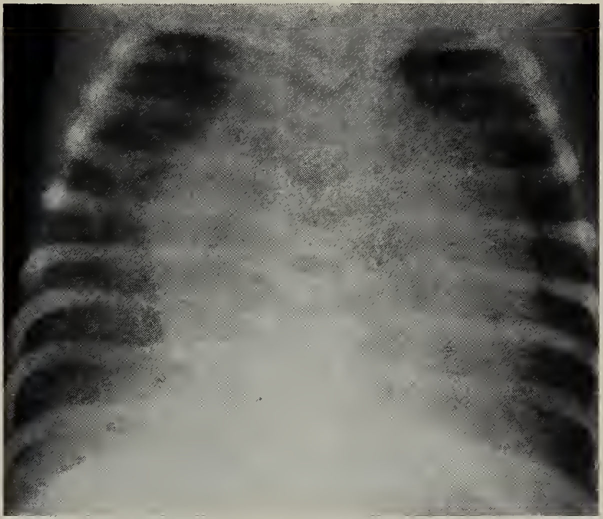

Figure 6.—Hypoplastic left heart in an eight-day-old female with tachypnea and dusky cyanosis since the second day of life. Electrocardiogram: Right ventricular hypertrophy. Roentgenogram: Enlarged heart with enlarged right atrium and pulmonary outflow tract, the latter contributing to the high convexity of the left heart border. The pulmonary vasculature is increased with interstitial pulmonary edema. Necropsy: Mitral atresia, hypoplastic left ventricle, small ventricular septal defect, atrial septal defect and patent dustus arteriosus.

with cyanosis and respiratory distress within the first few days of life. Patients in whom the total anomalous pulmonary venous return is without obstruction (most often with connection above the diaphragm), usually remain asymptomatic until a later period. The electrocardiogram is consistent with right ventricular hypertrophy, which may be pronounced. The roentgenographic appearance of the chest is strongly suggestive of this entity. Although the lungs reveal evidence of interstitial pulmonary edema, the size of the heart is normal[8] (Figure 7). Thickening of the fissures strongly suggests pulmonary edema. Indentation on the anterior aspect of the barium-filled esophagus immediately above the diaphragm, but below the left atrium, is caused by the anomalous vein. It too is strongly suggestive of total anomalous pulmonary venous return below the diaphragm.[9] This entity must be differentiated from hyaline membrane disease, interstitial pneumonitis,[10] and pulmonary lymphangiectasia.[11]

Myocardiopathy

In newborn infants with endocardial fibroelastosis[12] or myocarditis,[13] congestive heart failure may be present. Myocarditis, usually caused by Coxsackie B virus, may be secondary to an epidemic in the newborn nursery. The electrocardiogram in both diseases usually is indicative of left ventricular hypertrophy. Frequently, ischemic changes are demonstrated, manifested by ST and T wave changes in the left precordial leads.

The roentgenogram of the chest reveals a nonspecifically enlarged heart with pulmonary vasculature which may be normal initially, but eventually shows signs of congestive heart failure (Figure 8).

High Output Failure

Peripheral arteriovenous fistula. Peripheral arteriovenous fistula, usually cerebral in location, often is manifested in signs of congestive heart failure and mild cyanosis in the first two weeks of life.[14] The electrocardiogram is consistent with right ventricular hypertrophy.

The most important clinical feature to be sought in any newborn infant with congestive heart failure, especially when a significant cardiac murmur is absent, is the presence of a bruit over the organ containing the arteriovenous fistula, usually the head.

The roentgenogram of the chest shows pronounced enlargement of the heart with pulmonary vasculature which may appear normal initially but later shows signs of congestive heart failure with pulmonary edema (Figure 9).

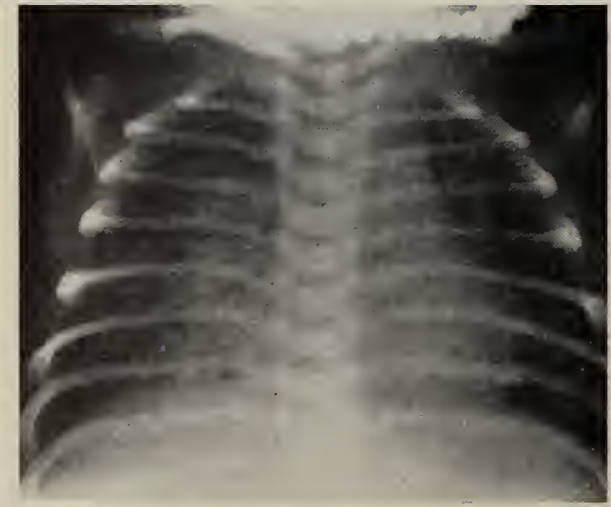

Figure 7.—Total anomalous pulmonary venous return to portal vein (necropsy) in a four-day-old female, cyanotic since birth, with congestive heart failure at four days. Electrocardiogram: Right ventricular hypertrophy. Roentgenogram: Typical appearance of severe pulmonary edema with pronounced reticulonodular pattern and hazy vascular margins. The size of the heart is normal (contrast to Figures 5 and 6). (Roentgenogram, courtesy of Hooshang Taybi, M.D., Children's Hospital Medical Center, Oakland, Calif.)

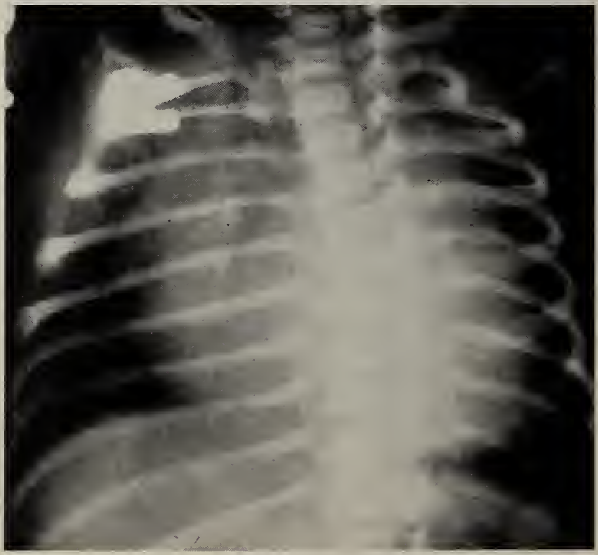

Figure 8. — Myocarditis and widespread myocardial fibrosis, cause unknown (necropsy), in a 13-day-old female in whom congestive heart failure and mild cyanosis developed at five days of age. Electrocardiogram: Right ventricular preponderance. (Most of the patients with myocardiopathy have electrocardiographic evidence of left ventricular hypertrophy.) Roentgenogram: Decidedly enlarged heart with normal pulmonary vasculature and no evidence of pulmonary edema despite clinical congestive heart failure.

Hypervolemia. Some infants have signs of plethora, cyanosis, and respiratory distress caused by the fetal transfusion syndrome.[15] The transfusion from the placenta or a twin causes hypervolemia, resulting in congestive heart failure in the neonate. The electrocardiogram is normal in most instances. As the plasma volume decreases, the hematocrit becomes elevated.

Roentgenograms of the chest show changes consistent with cardiac enlargement and there are signs of congestive heart failure and interstitial pulmonary edema (Figure 10). The results of cardiac catheterization and angiocardiography are normal except for elevated end-diastolic pressures in both ventricles. Since the primary cause of distress in these infants is excessive blood volume, phlebotomy may be lifesaving. As the blood volume is reduced, the size of the heart and pulmonary vasculature return to normal (Figure 11).

Right-sided Obstruction

Pulmonary stenosis or atresia with intact ventricular septum. Severe pulmonary stenosis or pulmonary atresia with intact ventricular septum may be associated with cyanosis in the immediate newborn period.[16-19] The electrocardiogram in severe pulmonary stenosis reveals severe right ventricular hypertrophy. In pulmonary atresia with intact ventricular septum, the electrocardiographic abnormalities are those of left ventricular hypertrophy in four-fifths of these patients and right ventricular hypertrophy in one-fifth, both related to pronounced difference in right ventricular size.[1]

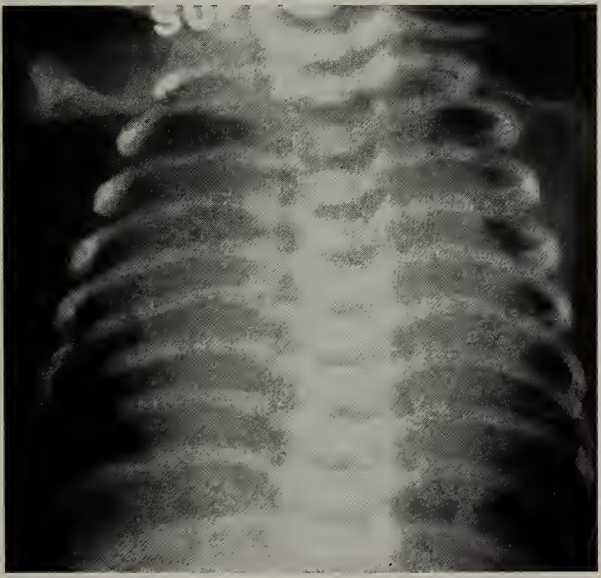

Figure 9.—Cerebral arteriovenous fistula (necropsy) in a four-day-old female with congestive heart failure soon after birth. A cutaneous hemangioma was present beneath the right eye and a continuous bruit was audible over the head. Electrocardiogram: Right ventricular hypertrophy. Roentgenogram: Massively enlarged heart with normal pulmonary vasculature and no roentgen evidence of pulmonary edema despite clinically evident congestive heart failure.

Roentgenograms of the chest show cardiac enlargement with decreased pulmonary vasculature (Figure 12). The left heart border may be hemispherical.[18] Immediate surgical correction may be lifesaving.

Severe tetralogy of Fallot. Tetralogy of Fallot is a rare cause of cyanosis in the newborn period except in instances of severe pulmonic stenosis. The electrocardiogram is consistent with right ventricular hypertrophy.

In this age group roentgenograms of the chest show normal heart size, and the typical boot-shaped configuration may not be present. The pulmonary vasculature is decreased. Approximately 25 percent of patients have an associated right aortic arch, which usually deviates the trachea toward the opposite side.

Tricuspid atresia. With tricuspid atresia, cyanosis is usually present in the immediate newborn period. The electrocardiogram is strongly suggestive of the diagnosis, with changes indicative of left ventricular hypertrophy and left axis deviation.

The roentgenogram of the chest most often shows a normal-sized heart with decreased pulmo-

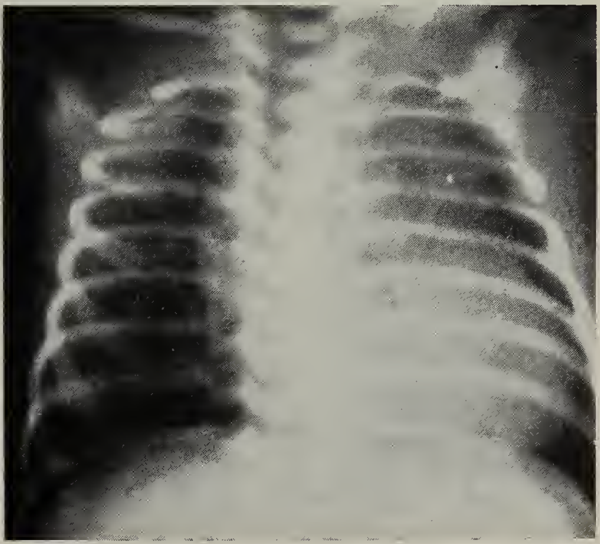

Figure 10.—Hypervolemia syndrome in a one-day-old female with congestive heart failure in the first day of life. Electrocardiogram: Normal. Hematocrit rose to 75 percent. Cardiac catheterization and angiocardiogram substantiated the diagnosis. Roentgenogram: Slightly enlarged heart with interstitial pulmonary edema.

nary vasculature. The electrocardiogram distinguishes this entity from severe tetralogy of Fallot.

Discussion

Congenital heart disease causing newborn respiratory distress or cyanosis, or both, is a difficult diagnostic problem. Close communication between the radiologist and pediatrician is necessary to achieve optimal results, accomplished by correlating the clinical, electrocardiographic, and roentgenographic findings. Certain congential heart lesions such as complete transposition of the great vessels, hypoplastic left heart, total anomalous pulmonary venous return below the diaphragm and severe right-sided obstructive lesions, commonly cause cyanosis or newborn distress. Other congenital heart lesions, such as atrial septal defect, ventricular septal defect and patent ductus arteriosus, usually do not result in this distress because the left-to-right shunt is limited in the newborn period by the normally high vascular resistance of the lung.[2] On careful consideration of the clinical features, the electrocardiogram, and the chest roentgenogram, the nature of the congenital heart lesion is usually determinable. Prompt cardiac catheterization and angiocardiography are necessary to completely define the pathologic change, facilitating early therapy.

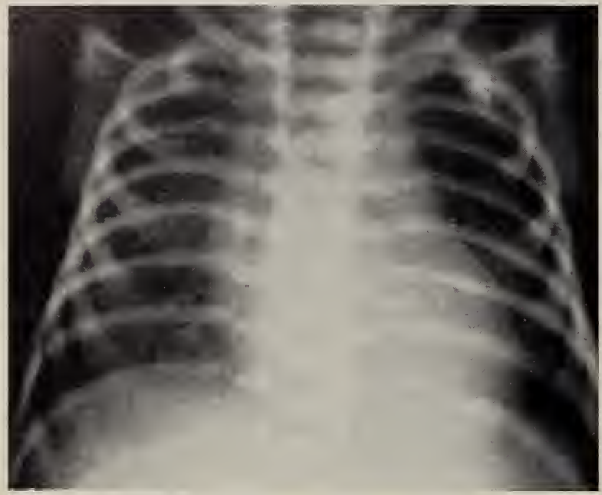

Figure 11.—Hypervolemia syndrome, improving. Same patient as Figure 10 at four days of age, with clinically improving congestive heart failure after phlebotomy. Roentgenogram: Heart size returned to normal with pulmonary edema still evident but improving.

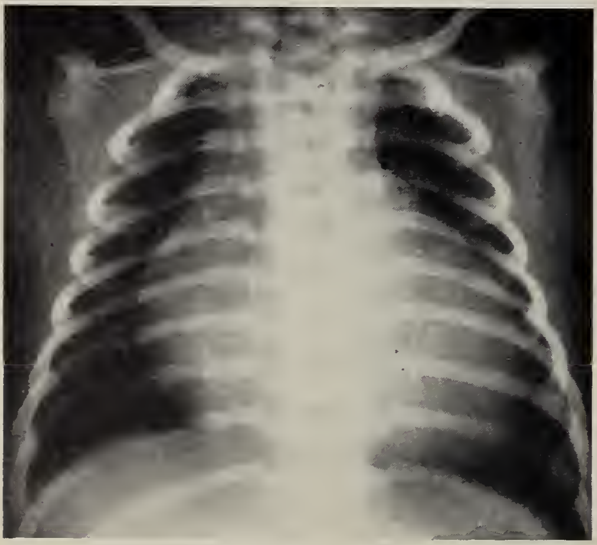

Figure 12.—Pulmonary atresia with intact ventricular septum in a four-day-old female with cyanosis and congestive heart failure since two days of age. Electrocardiogram: Pronounced right atrial and right ventricular hypertrophy. Roentgenogram: Decidedly enlarged heart, prominent right atrium, and decreased pulmonary vasculature. (Roentgenogram, courtesy of Hooshang Taybi, M.D., Children's Hospital Medical Center, Oakland, Calif.)

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Immunization for Children

Motivating Families to Complete a Series

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■ *A communication gap in transmission of information from health professionals to indigent parents is demonstrated by the incomplete immunization of children attending pediatric health facilities. To bridge this gap, young women of similar ethnic and social backgrounds were recruited and trained briefly in counseling parents concerning adequate immunization.*

The effectiveness of these Health Aides in motivating parents to complete an immunization series was less than that of Public Health Nurses. Even so, the Aides were able to motivate two-thirds of the families that they counseled.

Conclusions were that a significant number of children appearing in a large public emergency room facility are unimmunized. Many of these children are not seriously ill and an immunization series can be initiated "on the spot." Motivation to complete the series can be done almost as satisfactorily by young rapidly trained indigenous Health Aides as by professionals.

ALTHOUGH POTENT VACCINES have been developed against many of the infectious diseases, a significant segment of the population has not been reached by the present methods of delivery of these agents. Only two-thirds of California pre-school children have been immunized against smallpox, diphtheria, tetanus and pertussis.[1] Of the children presenting for care in the Pediatric Emergency room (ER) of the Los Angeles County-University of Southern California Medical Center, only 57 percent are completely immunized against poliomyelitis, diphtheria, tetanus and pertussis.[2]

These immunization deficiencies may be due to many factors: Lack of motivation of the parent; professional failure to inform the parent effectively about the vaccines available; general ignorance of good health practices; cultural patterns[3]; isolation of ethnic groups[4]; inability to make decisions readily[4]; and the confusing fragmentation of systematic medical care offered by social agencies.[5]

Health agencies have attempted to reach the unimmunized population through mass media (television, radio, newspapers, public posters) in various combinations. These techniques have not

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This study was supported by the Children's Bureau, Department of Health, Education, and Welfare, Grant H 117.

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Submitted, revised, 18 September 1968.

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proved particularly effective in low income areas.[6,7]

Lack of response to local health department activities was demonstrated in our own Outpatient Department activities in 1966.[8] The Los Angeles County Health Department set up an immunization clinic in the Pediatric Outpatient Department (OPD) of the Los Angeles County-University of Southern California Medical Center. Public Health Nurses and clerks screened the immunization records of as many pediatric patients as possible and initiated needed immunizations for siblings as well as patients not acutely ill. The parent was given a choice to return for completion of the series, either to the Pediatric OPD or the Public Health Center closest to his residence and a definite appointment was arranged at a convenient time. Of those to return to the hospital, 48 (56 percent) of 86 patients kept return appointments at the Pediatric OPD. Only 39 (27 percent) of 144 referred to the Health Department appeared at the health centers, and of the remainder, 31 returned to the Pediatric OPD regardless of their initial choice. These data indicated that a medical center, dispensing curative as well as preventive care, may have some advantage over the traditional Public Health Center as an effective site for immunizations, even though geographically less convenient.

The inability of professional medical personnel to communicate health information adequately to uneducated, and often disinterested and hostile parents from the lower social classes, may play a part in perpetuating ignorance of health practices. Fink[9] noted that only 21 percent of patients attending a general pediatric clinic understood the nature of their illness, 30 percent took medication as directed, and 23 percent followed prescribed procedures. If a "special" Public Health Nurse or physician were employed, still only 65 percent understood the problem, 73 percent took prescribed medications and 83 percent carried out procedures. Bergman,[10] Maddock,[11] and many others[12,13] have noted the failure of up to 65 percent of the patients to take medications reliably. Korsch[14] pointed out that lack of communication between clinic physician and parent leads to dissatisfaction and failure to comply with instructions.

Indigenous Health Aides, often from the minority populations served, have been utilized in many situations to break down ethnic and social communication barriers. Aides have been trained to function usefully as home managers in rural[15] and metropolitan[16] areas; as public health nurse assistants[17]; as translator, advocate, and coordinator of social services[18]; and even as a provider of direct medical care in a remote Alaskan area with only radio contact with physician supervision.[19] Reiff and Reissman emphasized the ability of the indigenous Aide to speak the language of the social class, to understand cultural problems, and to relate successfully to minority ethnic groups.[20]

Several questions about the utilization of Health Aides remain unanswered objectively: How much training is required to make the Aides effective, yet not alienate them from the population they propose to serve? If over-trained, will an Aide turn to the technical language and professional attitude of the physician instead of using the colloquial language of the patient? Do natural skills decrease as professional skills and loyalty increase? What level of previous education should an Aide have obtained? Can a drop-out from high school with faulty study habits be trained to dispense technical knowledge? What is the ideal age range and the degree of practical experience in child care necessary for acceptance of the Aide by the parent?

The Study

To supply answers to these questions we proposed to (1) measure and compare the motivation of parents to return to the Pediatric Outpatient Department for the immunization of their child when instructed by Public Health Nurses or by indigenous Health Aides; and (2) determine whether a relatively short period of on-the-job training of young Aides, such as may be obtained from the Neighborhood Youth Corps or the Youth Opportunity Unit of Civil Service, is significantly effective in motivating parents for disease prevention.

Sample Population

The Pediatric Emergency Room had 32,753 patient visits between 8 a.m. and 4 p.m. during the period of this study (September 1966 to November 1967). The patients ranged in age from one day to fifteen years. The ethnic distribution was 56 percent Negro, 30 percent Mexican-American and 14 percent Caucasian.

Half of the families were on welfare. The unemployment rate of the father, if present in the family, was 30 percent. Almost 25 percent of the children under five years of age had an iron deficiency anemia. The population is highly mobile: 77 percent of the Negro families, 73 percent of the

Caucasians, and 60 percent of the Mexican-Americans had moved to the Los Angeles Area within the preceding five years. The extent to which the families utilized public facilities was demonstrated by the birth of 86 percent of the Negro children, 75 percent of the Mexican-American, and 60 percent of the Caucasian pediatric patients in a local public hospital. Forty-six percent of the patients had had over four previous visits to our Emergency Room.

The diseases observed were not unusual or severe. By the examining physician's judgment, 10 percent of the children were completely well or only slightly ill; 63 percent had a very mild illness; 25 percent were moderately ill; and only 2 percent were considered seriously ill. Approximately 35 precent of the illnesses were upper respiratory tract infections, including otitis media.

This population, therefore, represents an indigent, largely minority group accustomed to using public facilities, but inclined to seek medical attention for a child only when it becomes ill. The mild minor illnesses observed do not preclude initiating immunization or providing a recall injection ("booster") at the time of a casual ER visit.

Obtaining the Training Health Aides

Through the cooperation of the Youth Opportunity Unit of Civil Service and the Neighborhood Youth Corps, seven Negro and three Mexican-American women, ranging in age from 18 to 20 years, were enrolled in the program. All had completed high school. Five were married and had children but were separated from their husbands. One participant was dropped from the program because of intercurrent illness. None had criminal records.

The results of the study are based on the combined work of these Aides.

Two Public Health Nurses and a pediatrician instructed the Aides didactically two hours daily for one week concerning the protective value of immunizations, the number of injections required, correct dosage of poliomyelitis vaccine, interval between boosters, and possible reactions to the various vaccines. The Aides kept written notebooks for future reference.

The instructors used few technicals terms in teaching the Aides, hoping that the Aides would retain their colloquial, idiomatic language when in contact with parents.

This form of teaching did not hold the attention of several of the Aides. Reissman[20] has noted that on-the-job training is superior to classroom instruction for teaching at this level.

During the next three weeks, the Aides accompanied the Public Health Nurses in the ER, observing the nurses' methods in dealing with parents and their children and instructing parents under the nurses' supervision. After that time, the Aides were on their own, with the prerogative to use any method possible to influence parents to complete an immunization series.

During the course of the study, we designed simple literature as a teaching aid which might be used to reinforce the oral presentation. No word in this literature had over three syllables. Sentences were limited to ten to twelve words. The text was edited for understanding by the Health Aides themselves, together with other indigenous aides and clerks in the Outpatient Department.

Procedures

An Aide was stationed at the entrance to the examination rooms from 8 a.m. to 4 p.m., Monday, Wednesday and Friday. After patients had registered for care, the Aide obtained and recorded the history of previous immunizations from the parents. Children were considered eligible for immunization if they were over two months of age and had not had immunizations initiated elsewhere within the preceding three months. Siblings who accompanied the patient were screened similarly. The Aide, unassisted, determined what immunizations were required, and gave a record of this to the parent. The Aide then attempted, in her own words, to convince the parent of the importance of protection against infectious diseases.

Thereafter, the patient was examined in the ER. If the examining physician felt that the child was not too ill to receive an immunization, he approved the record by initialing it.

After the patient had been examined and treated, the Aide either brought the child to a nurse for vaccination or injection or personally administered poliomyelitis vaccine on a sugar cube.

After the vaccine had been administered, the Aide gave the patient a return appointment in writing, in either English or Spanish, for a specific day. The patient could appear anytime between 8:30 a.m. and 3:30 p.m. on that day.

The name of the Aide or Public Health Nurse and the telephone number were included on the slip and the family was asked to call for another

TABLE 1.—*Individual Response to Scheduled Appointments.*

Category of Return Visits	*Public Health Nurse 1213 Scheduled Appointments*		*Health Aide 911 Scheduled Appointments*		*2124 Total Scheduled Appointments*	
	No.	*%*	*No.*	*%*	*No.*	*%*
Returned with no reminder	677	56	429	46.9*	1,106	52
Returned with one postcard	204	17	152	17	356	17
Total returned spontaneously or with first reminder	881	73	681	64†	1,462	69
Returned with second reminder	(a)		(a)		222	10.4
Total individuals returned	(a)		(a)		1,684	79.4

Comparison of Public Health Nurse and Aide: *$X^2 = 15.5$ $p < 0.001$, †$X^2 = 18.6$ $p < 0.001$.
(a) Nurses only sent second reminders: either a postcard, telephone call or telegram.

TABLE 2.—*Family Response to Scheduled Appointments.*

Category of Return Visits	*Public Health Nurse 859 Scheduled Appointments*		*Health Aide 627 Scheduled Appointments*		*1486 Total Scheduled Family Appointments*	
	No.	*%*	*No.*	*%*	*No.*	*%*
Returned with no reminder	473	55	300	48	773	52
Returned with one postcard	141	16	102	16	243	16
Total returned spontaneously or with first reminder	614	71	402	64†	1,016	68
Returned with second reminder	113	8	(a)		113	8
Total families returned	..		..		161	77.7

Comparison of Public Health Nurse and Aide: *$X^2 = 7.27$ $p < .01$, †$X^2 = 8.75$ $p < .01$.
(a) Nurses only sent second reminders: either a postcard, telephone call or telegram.

appointment if they were unable to return on the specified day. The parents responded surprisingly frequently, and often spontaneously informed us if they planned to follow up the immunization series with a private physician or a Public Health Clinic visit.

On Tuesday and Thursday, three Caucasian Public Health Nurses followed the same procedures in the Emergency Room, but used a standard method of parent instruction. The group so instructed was used as a control.

Since the population we were dealing with frequently has transportation problems, we allowed seven days past the scheduled day before initiating follow-up procedures. In all cases, the first follow-up consisted of a hand-written postcard which was written by the person who had given the appointment to the patient. The Aides composed their cards without supervision. The new appointment was scheduled seven days later. Again, a week was allowed before the appointment was considered broken.

The second follow-up was always done by the Public Health Nurses. If the patient had a telephone, the Public Health Nurse called to arrange a new appointment date with the parent. If the patient did not have a telephone or could not be reached by phone, the nurse mailed another appointment by postcard. In a few cases, the nurses sent an appointment by telegram to test the efficacy of this method.

If the patient did not return after the second follow-up, he was dropped from the study.

Results

Results were tabulated both as to individual visits (Table 1) and as to family visits (Table 2), since many families had more than one child receiving immunizations.

Table 1 indicates that of 2,124 individual patients receiving an appointment for an immunization, 1,106 (52 percent) returned within a week of the scheduled appointment day without requiring further reminder. A single postcard sent to the remaining 1,018 increased the number returning to 1,462 (69 percent). A second postcard brought the total individual returns to 1,635 (77 percent). The time-consuming telephone and expensive telegram recall procedures could add only 49 (2 percent) more (Table 3).

TABLE 3.—*Response to First Follow-Up of Missed Appointment.*

	Individuals		*Families*	
Response	*Sent by PHN*	*Sent by Aide*	*Sent by PHN*	*Sent by Aide*
Number sent first postcard	536	482	386	328
Number returned after first postcard	204	152	141	102
Percent responding to first postcard	37.9	31.4*	37.5	31.1†

Comparison of Public Health Nurse and Aide: *$X^2=4.46$ $p>0.05$, †$X^2=2.09$ $p>0.05$.

TABLE 4.—*Effectiveness of Methods of Recall.*

	Individuals		*Families*	
Method	*No.*	*%*	*No.*	*%*
Received one postcard.	1,018	. .	714	
Returned after one postcard	356	35	243	34.1
Received a second postcard.	500	. .	349	
Returned after second postcard	173	34.6	113	32.3
Received telephone call. . . .	109	. .	78	
Returned after telephone call	46	42.2*	31	39.7†
Received telegram	13 (a)		9	
Returned after telegram. . . .	3	23.1	1	11.1

*Comparison with 2nd Postcard $X^2 = 2.04$ $p > .05$.

†Comparison with 2nd Postcard $X^2 = 1.23$ $p > .05$.

(a) Two telegrams undeliverable.

Table 2 indicates a similar family response. Sixty-eight percent of the families returned spontaneously or with a single postcard reminder. With a second card, an additional 113 (8 percent) could be recalled and the telegram or telephone recalled another 2 percent.

A significantly greater proportion of those families motivated by the Public Health Nurses returned spontaneously or with one reminder, than those counselled by the Health Aides—55 percent against 48 percent. The family response to the first postcard follow-up is shown in Table 3. There was no difference in response between those reminded by an Aide-written card and those reminded by the Public Health Nurses.

A second postcard was as effective as a telephone call in recalling children for immunization (Table 4). The telegram appeared least effective. (These data must be viewed with caution since the families were not randomly selected for method of reappointment. A greater proportion of the families motivated by the Public Health Nurses returned spontaneously or with one reminder than those counselled by the Aides.)

Discussion

A pronounced change has occurred during the past few decades in the volume and nature of hospital emergency room visits. In large urban pediatric centers, the emergency room is being utilized as a non-scheduled, non-urgent general medical clinic for acute episodic illness, especially by the indigent "core city" population who do not seek or cannot get prompt attention from private physicians.[21] The emergency room has changed essentially into a community health station. Since this trend is unlikely to reverse in the immediate future, hospitals serving children who often lack adequate health supervision now are presented with an opportunity to improve the total health of this segment of the population instead of rendering the customary fragmented episodic care.

What functions can and should a large county hospital pediatric ER assume beyond rendering episodic acute care to an indigent population? Certainly in many instances the illness is so slight that it does not preclude initiating preventive health measures, such as immunization. We estimate that at least 20 percent of all our patients are well enough to receive immunizations and a similar situation elsewhere in the United States can be surmised from the data of other observers.[22-24] Thus, at least one forward step can be taken in converting episodic ER treatment into a semblance of comprehensive health supervision by immunizing these children whenever they appear.

Our Pediatric ER population includes many children who see the physician only when ill and who present the social and education characteristics of the hard-to-reach or the groups not responsive to public health measures. A pilot study indicated that many families, who received an initial immunization in our OPD, preferred to return here to complete the immunization series rather than visit a neighborhood health center.

Certainly the patients dealt with in the emergency room are not representative of the hard-to-reach. Many of those whom we immunized might have received vaccine eventually from the Health Department, in public school programs or through Head Start. Our efforts produced only 15 percent better results than those reported by the California State Department of Public Health.[1] However, without great effort, we were able to completely immunize (D-P-T, smallpox, poliomyelitis, and measles) 349 children in 14 months, and 1,327 more children are currently on the active roster of reappointments.

Regardless of the method of motivation or of parent recall, 20 percent of this population could not be inspired or persuaded to complete an immunization series in this clinic. Had we extended the reappointment time to include weekends or evenings, our 80 percent follow-up rate might have been higher. A previous study[25] indicated that many working parents, especially in minority groups, come to the ER at night when the family's only car becomes available. Traditional clinic hours may not meet the needs of a mother who works all day.[26] Other reasons for failure to complete immunization may be related to a basic lack of interest or concern,[27,28] to educational background,[28,29] to family or ethnic social values and prejudices,[4] to dissatisfaction with the outpatient care received on that day, and to general hostility.[30] Thirty-seven families transferred to private physicians' care or to a Public Health Center.

Thirty-five families changed residence, leaving no forwarding address. We may still be able to administer vaccine to some of the children of those families in the future if they reappear in the ER for acute illness.

The indigenous Health Aides did not prove statistically as effective as the Public Health Nurses in motivating families to return for completion of immunization. The Aides, although of similar ethnic and social status, apparently did not communicate more effectively with their peers than the Caucasian professionals. Factors influencing the failure to motivate more parents may be:

- The Aides were too young to appear authoritative or to command the respect of older parents. They actually were not peers of the families served.
- The training period was insufficient and the Aides lacked sufficient knowledge to be convincing. An extended period of training, probably on-the-job and not didactic,[20] may be necessary to teach fundamental facts and skills to this group.
- The communication gap may not be as wide as we believed and an experienced professional may speak the colloquial language adequately to motivate with relatively uncomplicated health instruction.

The Aides were far from ineffective, however; they induced 68 percent of their contacts to keep a follow-up appointment with either no reminder or use of a single postcard. The Aides were able to keep records successfully during the 14 months with a minimum of professional supervision.

A 4-cent postcard proved to be the most economical method of retrieving children for further immunization. The card seemed to be as effective as the telephone and required far less salaried professional time and effort. The results obtained by the telegram apparently did not justify the cost.

Consequently, we believe that a very inexpensive program of screening, immunization and follow-up using up to two postcard reminders can be installed readily in a large, busy Pediatric ER or Outpatient Clinic. A single supervising Public Health Nurse and two Health Aides (at much lower salaries than the professionals) can manage a program successfully and at relatively little cost.

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Beyond the Range of Sound

The Non-Otological Aspects of Deafness

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■ *Historically, deaf persons were seen as less than human — as "beasts of the field" who could not speak and thus had no legal rights. With educational advances, both the achievements of deaf individuals and the attitudes of the hearing world toward them have improved. However, the total scope of impairment of early profound deafness remains considerable despite vast advances in the fields of medicine, audiology and education. Traumatic parental reaction to the diagnosis and distorted parent-child communication may contribute to the impairment. Recent research has added to our knowledge of the social and psychiatric ramifications of deafness, but a lack of mental health professionals capable of communicating with deaf persons retards progress in this area.*

> All the animals that have been carefully observed behaved so as to confirm the philosophy in which the observer believed before his observations began. Nay, more they have displayed the national characteristics of the observer. Animals studied by Americans rush about frantically with an incredible display of hustle and pep and at last achieve the deserved result of chance. Animals observed by Germans sit still and think and at last evolve the solution of their inner conciousness.
>
> Bertrand Russell, *Outline of Philosophy*[1]

AS BERTRAND RUSSELL indicates, each national group sees animal characteristics through national eyes, each discipline views early profound deafness through its specialized frame of reference and with its own unique definition and focus. Generally it may be defined as a stress-producing hearing loss from birth or early childhood, rendering a person, incapable of effecting a meaningful and substantial auditory contact with the environment. However, deafness is more than a medical diagnosis with a drastically changing etiological picture and a proportional increase of prelinguistically deaf youngsters. It is more than a measured loss of hearing activity, now diagnosed with greater sophistication and earlier than ever before. It is a cultural phenomenon in which social, emotional, linguistic and intellectual patterns and problems are inextricably bound together.

Deafness of this type was described in ancient times and indeed, the first etiologic explanation of deafness was *divine displeasure:*

> And Jehovah said onto him, Who hath made man's mouth? or maketh a man dumb or deaf, or seeing or blind? Is it not I, Jehovah? (*Exodus* 4:11)

Early Christian writers followed suit, and St. Augustine questioned: ". . . from what source of culpability does it come that innocent ones deserve to be born sometimes blind, sometimes deaf, which defect indeed hinders faith itself, by witness of the Apostle who says, 'Faith comes by hearing.' "[2]

From the Langley Porter Neuropsychiatric Institute, San Francisco.

Research supported in part by VRA-RD-2408-S.

Presented before the Section on Otolaryngology at the 97th Annual Session of the California Medical Association, San Francisco, March 23 to 27, 1968.

Reprint requests to: Langley Porter Neuropsychiatric Institute, 401 Parnassus Avenue, San Francisco 94122.

Assumed causes such as these were not likely to produce an attitude of "tender, loving care" toward the afflicted. And indeed under both the Hebrew and the Justinian code of laws the deaf and the mute were without legal rights. The deaf were allowed to conduct their own affairs by means of writing only if they "had acquired language before their affliction."[2]

Deaf persons were usually seen with a mixture of awe, scorn, pity and fear. Aristotle saw them as the beasts in the field. He regarded the sense of hearing as the sense of instruction and concluded that those who lacked it had no capacity to learn. It was not until the sixteenth century that the first shadow of doubt was cast on this Aristotelian view. Cardano of Milan, an outstanding Renaissance physician, had devised ways to teach the deaf to learn. Unfortunately this brilliant man did not bring any of his theories to fruition.[3] However, during the same century the Benedictine monk Pedro Ponce de Leon succeeded not only in teaching several deaf scions of noble Spanish houses to read and write but, what was even more astounding, to speak.[4] Speech in that day was obligatory for true Christianity.

In the eyes of the law, speech was also obligatory to be "a person" and, as such, entitled to inherit property. Thus the second Spanish teacher, Juan Pablo Bonet, taught speech for legal reasons. But he held that the greatest need of the deaf was mental development and the major means toward this end was written language. Bonet used gestures, pantomime, signs and the manual alphabet, and he made deliberate use of lipreading.[4]

By now it was clearly demonstrated that rich, tutored, deaf noblemen could, unlike the beasts of the field, become persons — Christians, who could inherit their estates.

The masses of untutored deaf had to wait longer. Michel Abee de l'Epee (1712-1789) was the first to conduct a public school for all deaf children born in France or all of Europe. He differed from other brilliant practitioners in the art of teaching language to the congenitally deaf by "boundless charity and an open mind." He was not the first to note the existence of a sign language among deaf mutes—Montaigne two centuries earlier had been struck by its precision and rapidity. L'Epee was the first to attempt to learn it, use it and make it the medium of instruction for teaching French language and culture to the deaf mutes of his country.[5] The advent of public education for the deaf masses is a glorious monument to mankind. Unfortunately it brought in its wake one of the most bitter, prolonged controversies among professionals working with the deaf. Now that the deaf were declared human, professionals vied over the route they should take to become more human. One route was manual, the other oral. L'Epee used both in France. At the same time Samuel Heinicke in Germany and Thomas Braidwood in Scotland taught the oral method. For reasons not clearly understood, these routes were usually seen as mutually exclusive or contaminating, and angry letters flew back and forth.

In America, meantime, Thomas Gallaudet was engaged as a tutor for a young deaf girl. He wanted to learn how to help her most effectively. The teachers in England and Scotland were uncooperative, wanted their methods kept secret, so he went to France and studied with a student of l'Epee's. He returned a manualist, but the controversy was introduced into the United States and rages to this day. It is impossible to do justice to the controversy in this paper, but the controversy itself does not do justice to the deaf child caught in it. It is the method and not the pupil that takes the spotlight on this battleground. The conflict occasionally gives indications of all-out war, or of possible honorable peace with negotiation.

I have indicated that the deaf can be considered as a minority group, one of the most handicapped, living within two cultures—the deaf subculture and the larger hearing society. They can be seen as bilingual with varying degrees of competency in English (in its spoken or fingerspelled or written forms) and in the visual communication system of the American deaf, more commonly known as sign language. More about these competencies later. This subculture probably numbers 200,000 persons in the United States.[6]

My original entrance to this "community" was as a naive but trilingual psychology student and counselor among Arizona sunshine and palms and hundreds of deaf and blind youngsters. The blind were like thee and me; they spoke and related to others in ways which were familiar to me despite their major physical handicap.

The deaf, whose handicap was actually invisible, represented a somewhat foreign enclave, a minority group or subculture. Some of the deaf spoke and read lips with amazing skill, some did one or the other, and some did neither but had excellent reading and writing skills. All, however, communicated with intricate hand motions which appeared to have meaning since the ordinary daily tasks continued smoothly, people acknowledged each other, understood each other, validated each other, obtained material things for and from each other, and responded emotionally to one another. The messages certainly were sent, received and interpreted. But not by me. Again for the third time in my life I found myself among people who "spoke" a language I did not understand. And for the third time, I learned a new language.

In many ways it was like learning French and English: a different vocabulary, a different syntax. But now it was my fingers that stumbled with an "accent" as previously my speech organs had.

Who are the deaf? Who are the 200,000? They are Americans who share certain "statistical" characteristics. They are of normal intellectual potential. Many research studies indicate that there is no causal relationship between deafness and intelligence potential.[7] There are, however, tragic and numerous indications that most deaf adults do not live up to this normal potential. Educational achievement studies indicate that there is a three to four year language gap (English); the average deaf person reads at fifth grade or below; only 12 percent are said to achieve linguistic competence. Only 4 percent are proficient speech readers or speakers, and there are no studies to indicate a causal relationship to intelligence.[8]

Although estimates indicate that 78 percent of the adult deaf use the sign language,[9,10] there are no studies to indicate linguistic competence in this language. No tests exist regarding the language of signs, and only recently has the visual communication system of the American deaf been subjected to linguistic analysis.[5]

The personality characteristics of the deaf *in toto* are said to have a certain uniqueness. The most prominent finding appears to be "emotional immaturity." Levine[11] described this complex in terms of egocentricity, easy irritability, impulsiveness and suggestibility. Myklebust[12] found the deaf immature in the area of "caring for others" (as per the Vineland Social maturity scale). Altshuler[13] saw the deaf as showing egocentricity, a lack of empathy, an adaptive approach characterized by gross coercive dependence and behavioral manifestations of impulsivity and little thoughtful introspection.

The vocational picture is restrictive—88 percent of deaf males are employed in manual labor—almost two or three times the proportion for the hearing population. Conversely only 17 percent of the deaf population are employed in white collar jobs—professional, technical, managerial, clerical and sales—as compared with 47 percent of the general population of the United States.[10] Once employment is found, the deaf are stable in job tenure.[10,14] Employers report satisfactory work records.[15] Despite this exemplary work record it is not uncommon to find employment practices that are discriminatory against deaf applicants.[16,17]

The social and marital adjustment is also relatively stable. Most deaf persons marry, and most marry deaf mates.[18] Most of the marriages are reasonably stable, most of the children born to the deaf are hearing—only 10 percent are deaf. The 200,000 lead active social lives—67 percent belong to deaf organizations.[10] There are deaf churches, clubs, newspapers and even Deaf Olympic Games.

The social-psychological profile of the 200,000 has not done justice to the diversity which exists within all groups. Not all deaf persons, for example, show intellectual, educational or communicative retardation or the emotional uniqueness described above. Some of them are either outstandingly gifted or their parents have made heroic and successful efforts. They are few indeed and further study of them is merited.

There is a growing body of evidence, however, that one group of deaf people may indeed do better than others. These are the deaf children of deaf parents, who account for 10 percent of the deaf population. Deaf children of deaf parents have been found to show "better adjustment,"[19] a higher educational level and better command of language,[20] significantly higher reading scores, speechreading scores and written language scores[21]; higher scores in fingerspelling and vocabulary.[22] Meadow[23] found that deaf children of deaf parents have significantly higher achievement test scores and significantly higher teacher counselor ratings on items relating to maturity, responsibility, independence, sociability and appropriate sex role behavior. Furthermore, they received higher ratings for facility in written language, receptive and expressive fingerspelling, absence of communicative frustration, and willingness to communicate with strangers. No differences were found for speech and lipreading ability.

What are the significant differences? Clinical studies, experimental evidence, and anecdotal material indicate that the interaction of deaf parents and their deaf children may be decidedly different from that of hearing parents and their deaf children. These differences in interaction may be traced to differences in early parent-child communication, and in reaction to the diagnosis, with subsequent coping mechanisms affecting patterns of child-rearing.

Let us consider, first, the matter of early parent-child communication. To reiterate, most deaf adults use the manual sign language, and most marry deaf mates. Furthermore, it would appear that most deaf parents use sign language with their deaf and hearing children. Stuckless and Birch[21] find that 64 percent of deaf parents use the language of signs with their infants, and only 5 percent state they do not use signs with their older deaf children. These deaf children may be the only ones who learn a language easily, playfully, as a "mother tongue."

Children who can hear, regardless of culture, and almost regardless of intelligence quotient, develop linguistic competency by age five. Their vocabulary ranges from 5,000 to 26,000 words and they have an excellent command of the complex syntax of the English language.[24] The typical deaf child of five may have no symbol system available to him until much later. He may not know that objects have labels. He certainly does not know how to manipulate these symbols into meaningful sentences. It is true that some educators state that if speech and speechreading are taught effectively, the communication void will be filled. However, this has not come about despite truly Herculean efforts on the part of dedicated teachers and parents.

The deaf child of deaf parents is, however, learning a language at a very early age which might indeed be the critical age for language development. The mode of acquisition is almost totally unknown except through anecdotal material. There exists no standardized test to assess its knowledge. The deaf child's knowledge of symbol formation is usually tested by investigators unacquainted with the sign language who judge the response solely in terms of spoken English. Spanish-speaking children have in the past been similarly tested only by English-speaking investigators. Experience in the New York school system suggests that both English and Spanish may be enhanced if the school makes its overtures to the Spanish-speaking pupils by teaching Spanish.[25] Psychiatric evidence suggests that speech itself may be enhanced if sign language is also accepted.

Ervin-Tripp,[25] in a thorough summary of research findings, discusses "influences on language development" under the headings of organic readiness, social interaction, opportunity for imitation, and comprehension. She traces language development from prelinguistic vocalizations (similar in hearing and deaf infants up to the age of three months) to linguistic productions. There is no systematic study of early motor equivalents of a deaf infant learning the sign language. In fact, there have been almost no studies of cognition and behavior of the deaf child before school age.[5] Anecdotal material, case histories, and personal observations indicate that the deaf or hearing child of deaf parents goes through a series of organized steps in the acquisition of the sign language. These steps include motor control of the hands, accurate perception of body parts necessary for correct reception and expression of a "sign" as analogous to a "word." For example, the sign "dog" is a quick, repetitive motion of the palm of the hand on top of the knee; "girl" is the thumb of a fisted hand stroking over the cheek; "boy" an extended hand held in salute to the forehead with rapid opposition of the thumb to the palm (as if removing a cap). All require a knowledge of correct motion and position in space. A thorough study of the acquisition of receptive and expressive language in any form in the young deaf child may have great theoretical and practical implication for the early rearing of deaf infants.

In addition to the consideration of early parent-child communication, the early parental reaction to the diagnosis and subsequent coping mechanisms are also of crucial importance to the deaf child.

Congenital deafness is an invisible defect which is easily overlooked by parents. Furth[8] indicates that the typical parent of a deaf child does not suspect the disability until age one and a half, and that the typical definite diagnosis is not made until three years of age. Despite recent advances which enable audiological diagnosis within the first three months, there are many undiagnosed and misdiagnosed cases from earlier times. Some studies indicate that the "well adjusted" parents are more likely than others to overlook the disability. This is attributed to the mechanism of denial.[26] My own clinical experience corroborates the delay but postulates a successful nonverbal communication pattern between the "well adjusted" parents and their deaf children, which in turn delays the diagnosis.

The diagnosis of a defect in a child is frequently followed by "diagnosis shopping." There is some evidence that up to 60 percent of parents of deaf children will visit at least four physicians before understanding or accepting the diagnosis of deafness. Some of these 60 percent, however, indicated that the physicians had not accepted their hunch about the child's deafness.[23] Deaf parents of deaf children appear to expect the diagnosis and to accept it at a much earlier age.

Parents of any defective child typically react to the diagnosis with shock, denial, guilt, and sorrow —sometimes chronic sorrow. This in turn may interfere with adequate mothering. There is some indication that parents of deaf children may deny or magnify the defect.

However, there is also some experimental and clinical evidence[23] that indicates that deaf parents of deaf children cope with the crisis of diagnosis more easily and quickly while their hearing counterparts prolong and intensify it. Even following the diagnosis Meadow[23] has found: "Deaf parents appear to be more comfortable with their deaf children, admit to fewer eating and toilet-training problems, and permit earlier independence and autonomy. Once the initial diagnosis is made deaf parents are less likely to seek conformity diagnosis, or a miraculous cure. There are indications that the oral-manual controversy . . . has an important effect on the approach to early socialization tasks by parents of deaf children regardless of hearing status."[23]

Thus, we are beginning to gain some understanding, both from research and from clinical experience, of the dynamics of family relationships which are so important to the eventual functioning of the deaf child and adult. More research is needed, and the lack of trained professionals in the mental health field who can communicate with deaf persons is a constant source of frustration to the few who are trying to meet the demand. There are indications that interest in this sub-group is growing, however. In the future we can hope that there will be adequate resources for referral of deaf patients and their families. Until that time, however, we can only hope for growing understanding of both otological and non-otological aspects of deafness in order to treat more effectively those individuals who are "beyond the range of sound."

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The Practitioner and Sch

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■ *The extraordinary plasticity of the growing child offers the general practitioner an unusual opportunity to intervene either in a preventative or therapeutic manner. Such intervention, properly the task of any informed physician dealing with families, can alter unhealthy growth to healthier development. The whole child is just as important as his medical illnesses; the whole family usually needs help when there is an emotional disturbance in any child.*

Common problems that lend themselves readily to physician intervention are behavior disorders accompanying a neurological deficit, conduct disorders, enuresis and school phobias. Knowing how to elicit information, to evaluate clinical data and to utilize the findings of a skilled psychologist, and when to refer to a psychiatrist, plus a thorough knowledge of community resources are part and parcel of a physician's equipment for dealing with children and families.

Child Problems

School age is an era of enormous growth physically and psychologically. Usually termed the latency period in the developmental schema, it is far from a quiescent period. Sexual and aggressive energies are normally released through motor activity. Witness the joy in rushing, tumbling, balancing, climbing, sliding; the rhythmical, chanting, repetitive games and sports which also foster peer relationships. Also, the school age child idealizes adults of action—ball players, firemen, policemen.

The grade school period is another painful step away from home and the dependent ties of infancy. The child is expected to master the educational skills of reading, writing and athletics, to develop a sense of industry and an increasing sense of self, of "who I am." A crucial task, little written about until recently, is the development of a feeling of solidarity with his peer groups and the building of common ideals. Without developing relationships to others, he becomes an isolated and lonely child. There is a better recognition of the "no's and don'ts" of parents and significant others, a growth and strengthening of conscience, of the sense of right and wrong. The fulfillment of the tasks of latency presupposes reasonable, healthy solutions of the psychological tasks of carefree childhood. An infant improperly cared for by a neglectful or rejecting parent, a child reared in many foster homes, or with a history of feeding disturbances, or with unusual difficulty achieving bowel control or urinary control, or with extraordinarily destructive behavior, or unusual sexual behavior will have difficulty with the job of latency until earlier tasks are resolved in a healthy manner.

Ways to recognize and to manage some of the common problems of this age period with which the practitioner has to deal are the subject of the communication. (Learning problems will not be discussed inasmuch as these require specialized attention and diagnostic procedures. Physicians confronted with such problems should refer them to psychiatrists or to psychologists for diagnostic testing or to child guidance clinics for appropriate study and management.)

Behavior Disorders with a Neurological Deficit

Billy was a cute, blond 7-year-old referred for disruptive behavior in class and at home. He was constantly in fights, had difficulty learning or staying with any project, and children avoided him. His mother, a pleasant young woman, was at her wit's end; the father was angrily impatient and perplexed. Results of a careful medical work-up, including neurological examination and electroencephalogram, were all within normal limits. The history, however, indicated Billy was a "blue baby" although born at term. Development appeared to have been average, although the parents had noticed he was very active, that he had become increasingly restless in nursery school and was easily frustrated and had a tendency to strike at things or persons. He was constantly "on the go" and had a limited attention span. The father described Billy as seeming to have "a pilot light burning under his tail" to keep him hopping. In the first grade

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Submitted 21 Dec. 1967.

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it was obvious to the teacher that the child had more than usual difficulty in recognizing letters and playing with his peers, let alone sitting quietly.

The foregoing clinical picture is quite typical of children with a neurological deficit or minimal brain dysfunction, and even though the results of the usual neurological examinations are negative, psychological tests performed by one skilled in administering them to children and evaluating the findings can demonstrate signs of organic impairment. Visual-motor tests (Bender Gestalt) are especially useful in such circumstances. The diagnostic process requires a careful history, which means knowing what to ask, a medical and neurological examination and sometimes an ophthalmic examination. For example, prematurely born children have subtle visual-motor deficits and neurologic impairment is evident in difficulty in learning to read, and in consequent behavior problems. Then a competent psychological evaluation is in order. A neurological deficit or minimal brain dysfunction does not mean mental retardation.

Although management of these troubled children varies, the essentials are fairly constant. Parents must be helped to understand the nature of the child's difficulty and the probability that in adolescence it usually will be compensated, that such a child requires an active physical program and definite, firm limits and structure, and that remedial help in school may be necessary, especially with reading. The judicious use of medication will help the child control himself. Dexedrine, up to 20 mg a day, often helps. One should begin with 5 mg twice a day and gradually increase it if necessary. With other patients methylphenidate (Ritalin®) 10 mg twice a day may be more effective. Where these do not favorably affect the child the use of chlorpromazine (Thorazine®) or thioridazine (Mellaril®) in varying amounts is indicated, and one should not hesitate to use large enough amounts to obtain an effect. The usual safeguards when giving any medication must be observed. Medication helps the child to be more tractable, thus more acceptable to parents, peers and teachers and results in a happier child with increased self esteem and attention span. Members of the patient's family should be questioned periodically as one means of observing the effectiveness of drugs, and medication can be gradually reduced and eliminated when it seems sufficient "braking power" has been internalized by the child. This varies for each child and his parents and one need not rush to discontinue the support medication gives.

Conduct Disorders

Children who suffer rejection, neglect or familial disharmony may display their unhappiness in disobedience, fighting, poor learning. These manifestations often reach such proportions that parents, or more usually the schools, demand something be done. Whether the pediatrician or family physician can manage the problem himself or must refer to a psychiatrist depends largely upon his own background of skills and the family's ability to understand and to help.

Jimmy, a 10-year-old, was seen in consultation because he constantly disrupted the class with his chattering and clowning. He was learning rather indifferently although he had good intellectual capacity. An older sister of 12 was fascinated by bullfighting and knew all about the leading toreadors. She used Jimmy to practice her passes; he was the make-believe bull and if he didn't cooperate she pummeled him. The family physician examined Jimmy and, finding nothing to account for his behavior, asked for a psychiatrist's advice.

The parents were delightful, infantile people whose quarrels reached fantastic proportions. The father, a perfectionistic, driving executive, was known for his awesome, choleric rages. Let one of the children step out of line or not come up to his standards, and there was a violent scene. Jimmy could not remember ever doing anything with his father that was fun. The mother was a pretty, quiet, sensitive woman who, in attempting to protect Jimmy, infantilized him and yielded to his whims. The housekeeper related that Jimmy did as he pleased whenever his mother made a request. If it was important enough, the mother then would shout her demand and the boy then would do what he had to do. The tensions and din at home were great. The parents said that they were "interested in and love our children" but that it seemed as if "in our differences" and "with our personalities" they had really forgotten the needs of the children and in effect had neglected them and "used them as our scapegoats."

Jimmy said he did not like to study but just to play, that he was stupid and that children in school "made" him talk and clown. A very engaging lad, he was unhappy, perplexed, insecure and sure he was as dumb as his father branded him in his more choleric moments.

The willingness and cooperation of the family and teacher made for a favorable therapeutic milieu. Sharing impressions, the psychiatrist and the family physician formulated the following plan. The family physician would meet weekly with the parents to attempt to alter the family interactions and help them understand the child's needs. He discussed the lad's problems with the school teacher, who was at her wit's end. With some thought of the possible benefit to her, Ritalin, 10 mg twice a day, was prescribed for the child, and to everyone's surprise the effect was miraculous. In two days, he could control himself in school and by the end of the week he piously told other children how ill behaved they were.

Jimmy's parents managed to keep their quarrels reasonably private and with some humor tried to ameliorate their frictions, which largely stemmed from inflated egos and immaturity. The father began to enjoy some activities with his son but stayed out of his school tasks. The mother learned to insist firmly that Jimmy do what she reasonably requested in tones that did not say "maybe." The teacher did remedial work with Jimmy for a time.

Once a month the psychiatrist saw Jimmy and noted steady improvement. Jimmy increasingly became a "regular" boy, was accepted in the Scouts, played baseball with his neighbors and proudly stated it was becoming easier "to be good in school." He showed off his homework and tests. The family doctor continued sessions with the parents weekly, together or individually as he saw fit, and discussed problems around the children. Medication was discontinued after six months. Whether it was the effective agent is questionable. It did help, one way or another.

As consultant, the psychiatrist was merely the "back-up" man. Are Jimmy's problems cured? One cannot say for certain. He and the family are improved and growing children have great plasticity and can repair well. Time and family perseverence will help.

School Phobias

A plaguing problem which should be treated as an emergency is that of the child who unaccountably fears going to school. Rather typically the patient is a lad who, on complaint of somatic symptoms, stays home. When coerced to go to school, apprehension mounts, somatic complaints increase. As anxiety increases, the lad refuses to go to school and if physically forced to do so will run away or be so obviously distressed he cannot remain or be held in school. One kindly principal held such a boy in his office after he had run out of class, and tried to sooth him. When the child, complaining of stomach pains, vomited over his office the principal quickly abandoned his good intentions.

The basic problem in "school phobias" is not fear of school but fear of separation from the maternal parent. The mother protests in all obvious sincerity that she wants her boy to go to school. The boy wants to go to school and gives many reasons why he cannot, saying that he gets sick but does not know why. He spends the day around the house, but after school and on weekends and during vacations he plays with other children just as he did before.

Why this separation anxiety? A careful history usually reveals previous evidence of anxiety upon separation on the part of both mother and child. Also, the mother has not permitted the child to be independent of her according to his age level. The panicky reaction on the part of the child is based on his fear that harm will come to his mother while he is away at school, that she will disappear. Closer investigation reveals the child is quite hostile to the mother and her demands that he be dependently tied to her; and he fears his angry thoughts may well destroy her. The father is perplexed by the child's anxious reactions and leaves the problem to the mother and the child after initial exasperation.

What precipitates this dramatic symptom complex? Often it seems to occur after an episode that threatens the mother, like an illness, a death in the family, possible marital separation, an accident or near accident. Or it may begin on returning to school after a summer vacation spent at home. Or there are no discernible overt factors, but rather anxiety, long building up, bursting forth. One 9-year-old had traced his panic to a storm which buffeted the plane on which the family was returning home. There was real danger that the plane might crash. At first he refused to go to school on cloudy days—it might storm. Soon he refused to go on any day when there was a cloud; and then if perfectly clear, for a cloud might appear. His basic apprehension was that his mother, a clinging, smothering woman, might get killed.

Management is difficult but obviously the school and family are factors. What is attempted at the Los Angeles County USC Medical Center is to put the child into hospital briefly, effecting a forcible separation, or have the parents enter the child into the day care program. This act of separation is in itself a significant therapeutic step. There is a school in the hospital, and school attendance is required. All the patients attend the school without much problem. This affords an opportunity to work intensively and separately with the child and the family while the pathological ties are ruptured by the period in hospital or significantly weakened by the day care separation. Such management is not feasible for the family physician.

Diagnosis is relatively simple. What to do? The answer is a resounding, "It depends." Parents physically coercing the child to school does not work. They rarely feel able to do this and often when the child is brought to school it is the mother, not the child, who has great difficulty at parting. Some therapists, intrigued by conditioning techniques, gradually accustom the child to going to school by getting him physically closer and closer to school, inside the school building, outside the schoolroom, then inside the room and gradually increasing time in the class until finally full-time regular attendance is reached. Others suggest home tutoring while working intensively with parents and child. Still others, while working with parents and child, suggest that the mother attend school with the child and then gradually increase her absence from class. The essential problem to be resolved is within the family and the special unhealthy ties between mother and child which make normal separation a frightening experience.

Probably the family physician cannot manage these problems without the help of a psychiatrist. Or the family may have to be referred for specialized psychiatric care. Recognition of the problem, explanation to the family and school authorities, and devising a method of continuing education of the child are first steps. Working with the child requires special skills and certainly working with parents about the nature of these problems will help them and possibly the child. In some cases a family physician, sustaining the family, the child and the school with poise, understanding and firmness, can gradually bring about a child's return to school. Often the child can be helped by the judicious prescription of anxiety-relieving drugs. There is a large variety of them and one may have to experiment. If a drug like hydroxyzine (Vistaril®) is not effective, one should not hesitate to use Thorazine®, but one should use adequate amounts. A positive, forcefully encouraging attitude on the part of the physician can be very effective.

Enuresis

Enuresis, preponderantly present in boys, has several factors behind it. First, it is a carryover from the infant years either because of decided infantilizing or, more often, deprivation of the child's needs. Second, battlegrounds between parents and child can be in many arenas—feeding and toilet training, for example. Third, training in economically or culturally poor areas may be very deficient. Fourth, there is always a hostile element in this symptom just as the vulgar expression signifies. Fifth, most often there is a sexual connotation too.

The usual history is that of a boy who has been sporadically wetting at night since infancy. Transitory enuresis following birth of a sibling is merely that—transitory, an infantile protest of "take care of me too as you do this unwanted arrival" (even if he pleaded previously, "I want a little brother.") He is described as sleeping heavily when the nocturnal event takes place, but soon it becomes apparent that, regardless of the time he is aroused to go to the toilet, he wets. Remedies like limiting fluids (which usually leads to piteous outcries of terrible thirst) are of little avail.

The enuretic child attributes his wetting to "bad kidneys," feels ashamed and quite hopeless about it, avoids staying overnight away from home or going to camp. Often accompanying the enuresis are conduct problems and indifferent school performance. With each failing effort at control, hopelessness increases.

Since in 99 percent of the children with enuresis there was no organic disease, cystoscopy should not be done. There must be more valid symptoms for so vigorous a procedure (usually construed by the child as a cruel and unusual punishment). The large number of ways mentioned to "cure" this symptom should make one suspicious that there is no specific answer. Shaming procedures are equally cruel. Scolding, mocking, making the child wash his clothes and bed linen only add to his sense of failure and defeat. Procedures like use of a bell apparatus to ring loudly when the sheet pad is wet, hauling the child to the toilet every three hours, and the like, are of little value. What is?

The closer to puberty the child with enuresis is, the more likely the doctor will be correct if he states, "He'll outgrow it." In most cases, enuresis ceases at puberty. After a medical and urine examination, one must explore the developmental history, the toilet training procedures and unusual events in the pre-school period (such as a stay in hospital, mother's illness, birth of a sibling, neglect by adult through disregard and self absorption, surgical procedures, unusual sexual experiences or exposure). The physician must inquire into what methods of management the parents have used.

The physician proceeds on two fronts. First, he carefully ascertains with the parents the probable factors in this symptom. Second, he helps with the management—which largely is accepting the wetting without censure when it occurs, but expressing confidence that it will eventually go. The child should be roused to void before the parents go to bed, which may be of some help. Sibling rivalries, seductiveness by either parent, viewing "girly" magazines, sharing the parental bed, unusual family frictions and the like are explored, and in sessions with parents the physician attempts to remedy obviously unhealthy situations. The child should be told candidly his symptom is not due to bad kidneys and is not hopeless but is a symptom expressing something like anger or wanting to be a baby. At times, by using stories like "I once knew a lad whose bed wetting came from etc., etc.," the physician can relate the suspected problem in a palatable way. This positive reassurance and a continued, positive attitude in periodic follow-ups does wonders for most enuretic children. Of course, the symptom may be one of a variety of symptoms in a seriously emotionally ill child, and in such circumstances a psychiatrist's intervention is required, but often a pediatrician or general practitioner, who is interested and who follows through and supports the family and child much in the manner described above, is quite successful in dealing with enuresis.

Conclusion

From the foregoing discussion of emotional problems of school-age children, some general principles can be formulated. The physician should and can do a great deal more with the everyday problems of the everyday child. He has first to be interested and then to learn about the average behavior of a particular age level. He can then tell when behavior constitutes a problem or symptom. Symptoms of this kind in children involve the entire family and affect its homeostasis. Treatment of the child requires involvement of the family, a fact familiar to general physicians.

Knowing how to elicit information and to evaluate data and clinical impressions, quite naturally leads to attempts at management which vary with the experience and interest of the physician. Implicit is the fact that one has to recognize just how much he himself is equipped to do, when to seek more specialized help, and how to utilize the findings of a skilled psychologist. Of utmost importance in dealing with families with children who have problems is to be thoroughly aware of community resources and how to use them.

Given the extraordinary plasticity of the growing child and an interested, concerned family, positive intervention can alter unhealthy growth to healthier development. Such intervention takes knowledge, interest and time and is properly part of the task of the physician just as much as other aspects of medicine are.

GENERIC AND TRADE NAMES OF DRUGS

Methylphenidate—*Ritalin®*
Chlorpromazine—*Thorazine®*
Thioridazine—*Mellaril®*
Hydroxyzine—*Vistaril®*

IN HEADACHE, EXAMINE THE HEAD

"Every patient that has a headache when he comes to you should always have an examination of his head, and by that I mean you should use your fingers and your vision; you percuss, you palpate, and you auscultate. Once in a while, you'll pick up a bruit and it's important."

—ARNOLD P. FRIEDMAN, M.D., New York City
Extracted from *Audio-Digest Otorhinolaryngology,* Vol. 1, No. 4, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

Viremia in a Recipient

JEANETTE WILKINS, M.D., MARGARET A. SALVATORE, B.A., JOHN M. LEEDOM, M.D.,
AND BERNARD PORTNOY, M.D., *Los Angeles*

■ *A live rubella virus vaccine, HPV-77 (High Passage Virus - 77 tissue culture passages) was administered subcutaneously to eight rubella-susceptible children housed in an isolation ward. One blood specimen, taken on the tenth day after vaccination, from one of the eight vaccines, yielded a rubella virus. This virus had laboratory markers which were "vaccine-like." To our knowledge, this represents the first isolation of rubella virus from the blood of a recipient of HPV-77 vaccine. However, the consistent antibody responses among vaccinees and the regular presence of rubella virus in their pharynges argue that viremia occurs in almost every susceptible recipient. The most logical explanation for the failure to document viremia in other recipients of HPV-77 vaccine is that the viremia is ordinarily low grade or transient or both.*

PV-77 Rubella Virus Vaccine

ISOLATION OF RUBELLA virus in tissue culture[1,2] provided the basis for the development of rubella vaccines. One live, attenuated rubella vaccine, designated HPV-77 (High Passage Virus-77 tissue culture passages) developed by Parkman and Meyer has received extensive experimental[3] and clinical testing.[4,5] However, viremia, easily demonstrated in natural rubella,[5] has not been detected in more than 500* human recipients of HPV-77 or HPV-77 derived vaccines,[4] although the vaccine virus is readily isolated from the pharynx ten to twenty days after immunization.[5] The first isolation of rubella virus from blood subsequent to injection of HPV-77 rubella vaccine is discussed below.

The Isolation, Virologic Methods and Study Design

The virus was isolated from the venous blood of J. Q., a 71-month-old mentally retarded child, ten days after subcutaneous inoculation of HPV-77 live rubella vaccine. His mental retardation was said to be "secondary to encephalopathy associated with prematurity." He had no known immunologic defects.

J. Q. was one of the group of 15 rubella-susceptible† children who participated in a study of HPV-77 vaccine efficacy at the Pacific State Hospital, Pomona, California. Eight of the children (vaccinees) in J. Q.'s group received 0.5 ml of HPV-77 rubella vaccine (grown in African Green Monkey Kidney [AGMK], Lot #P-77-Filling 4, Division of Biological Standards, N.I.H.). The remaining seven children (controls) did not receive the vaccine and were observed for evidence of transmission of the vaccine virus. None of the 15 children, including J. Q., had any clinical stigmata of rubella during a 67-day period of isolation.

For 37 days before the administration of HPV-77 vaccine, the 15 children in J. Q.'s group were kept under clinical surveillance in a special facility specifically designed for the isolation of children, and for 30 days after administration they were under clinical and virologic surveillance there. Egress and ingress to the study ward was controlled, and the 15 children did not have contact with any other patients, children or adolescents during the 67-day period. The isolation facility has separate eating and play facilities. Only persons (visitors and staff) previously shown to have

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From the Hastings Foundation Infectious Disease Laboratory, Departments of Pediatrics, Medicine, and Community Medicine and Public Health, University of Southern California School of Medicine, Los Angeles, and Pacific State Hospital, Pomona.

Supported in part by Contract PH-43-67-80 from the Vaccine Development Branch, Public Health Service Training Grant 5 T-1-AI-275 and Career Development Award 1 K-3-AI23,479 from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, and the Hastings Foundation Fund.

Submitted 26 August 1968.

Reprint requests to: Infectious Disease Laboratory, University of Southern California School of Medicine, 1200 North State Street, Los Angeles 90033 (Dr. Wilkins).

*Includes seven patients mentioned in this report.

†Susceptible = rubella neutralizing antibody titer of <1:2 and rubella hemagglutination inhibiting (HAI) antibody titer of <1:8.

both neutralizing and HAI antibodies against rubella were allowed on the ward.

Surveillance during the 67 days that these 15 children were on the special ward failed to detect natural rubella among Pacific State Hospital patients or personnel elsewhere in the hospital. The last known case of laboratory confirmed rubella occurring among patients at Pacific State Hospital had its onset on 2 May 1967, 76 days before the administration of vaccine to the 15 children. Further, no cases of natural rubella were noted during the six-month period following administration of vaccine to J. Q.'s group.

Monitoring of all 15 children covered a 30-day period after administration of the vaccine and included attempts to recover rubella virus from rectal swabs, throat swabs, and whole blood. Vaccinees were examined for virus in pharyngeal secretions and feces on days 1, 5, 7-16, 18, 20, 22, 25, and 30. Throat swabs and rectal swabs were obtained from control children on days 1, 7, 10, 15, 17, and 19-30. Approximately 5 ml of whole blood for virus isolation was collected in syringes, containing 0.1 ml heparin, from each of four vaccinees on days 1, 3, 8, and 9 after inoculation and from each of the remaining four on days 2, 7, 10, and 12. Whole blood, collected in the same manner, was obtained from each of four of the "control" children on days 17, 19, 21, and 23 and from each of the remaining three on days 18, 20, 22, and 24. All specimens for virus isolation attempts, including the heparinized blood, were placed in a portable dry ice chest, were immediately transported to our laboratory, and were stored at —70°C until tested.

The rubella virus isolation and identification procedures described by Parkman and coworkers[6] were employed, utilizing the pharyngeal secretions, feces, and slurries of the whole blood specimens. Each AGMK tissue culture lot used was tested for susceptibility to rubella virus, using a known strain.

The slurry of heparinized whole blood from J. Q., collected ten days after he was inoculated with HPV-77, yielded rubella virus on primary passage in AGMK.* This isolation was confirmed by recovery of rubella virus from the original slurry of whole, heparinized blood on primary passage in three separate lots of AGMK on three occasions in our laboratory. As added confirmation, Dr. Paul D. Parkman recovered a rubella virus from an aliquot of J. Q.'s original day 10 blood specimen.

Three other blood specimens from J. Q., drawn on days 2, 7, and 12 post HPV-77 inoculation, did not yield rubella virus on primary or secondary passage. None of the other 59 blood specimens from vaccinees or controls yielded rubella or other viruses.

One vaccinee, other than J. Q., yielded rubella virus. The organisms were isolated from throat swabs obtained on days 9 and 13. There were no other rubella virus isolations from vaccinees and none at all from controls.

Specimens for virus isolation (throat swabs, rectal swabs, and blood) were taken from other members of the study group on the day the positive blood specimen was obtained from patient J. Q., but none of them yielded rubella virus. Throat swabs collected from J. Q. on days 9, 12, 13, and 14 yielded rubella virus in secondary passage, in another lot of AGMK tissue culture, inoculated on a different date. The absence of other positive specimens, collected on day 10, and the absence of other rubella isolates in the "batch" inoculated into AGMK tissue culture at the same time as J. Q.'s day 10 blood specimen, would reduce the probability of accidental contamination of that blood during the times of either specimen collection or tissue culture inoculation.

Quantitation of the virus content in J. Q.'s day 10 blood specimen provided further evidence that the rubella strain isolated was not a contaminant. Titrations of the interfering doses$_{50}$ (InD$_{50}$) of the original specimen were done in AGMK tissue cultures, four tubes per dilution. Endpoints, determined by challenge with 100-1000 tissue culture infectious doses$_{50}$ of ECHO-11 on both the fifth and eleventh days after inoculation, were $10^{0.75}$ InD$_{50}$/0.2 ml and $10^{1.5}$InD$_{50}$/0.2 ml, respectively.

To investigate the possibility that J. Q.'s viremia was due to "wild" rubella virus, aliquots of 0.2 ml of the thawed slurry of the original, day 10, whole blood specimen were inoculated into a rabbit kidney tissue culture cell line (RK-13). HPV-77 characteristically produces CPE in RK-13 cells while low passage rubella virus usually does not.[7] Within eight days after inoculation, the cytopathogenic effect had progressed to complete destruction of the RK-13 monolayers. An interfering agent, identified by neutralization[6] as a rubella virus, was found when tissue culture fluid from the "positive" RK-13 tubes was passed into AGMK tissue cultures. These results were also confirmed by Dr. Parkman.

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*Rubella typing serum supplied by Dr. Paul D. Parkman, Laboratory of Viral Immunology, Division of Biological Standards, N.I.H.

Specimens of blood were collected from patient J. Q., his seven fellow vaccinees, and the seven controls on days 0, 15, 30, and 60 after administration of HPV-77 to the vaccinees. HAI and neutralizing antibody titers (Neut.) were performed by techniques described in the literature.[8,9] J. Q.'s titers were: (1) Day 0, HAI, <1:8, Neut. <1:2; (2) Day 15, HAI 1:32, Neut. 1:16; (3) Day 30, HAI 1:256, Neut. 1:128; (4) Day 60, HAI 1:256, Neut. 1:128. The other seven immunized children had rubella HAI and Neut. antibody titer rises of fourfold or greater by day 60, while titers of all seven contacts remained stable at <1:2 and <1:8, respectively, at day 60. Further, there were no detectable rubella complement fixing antibodies in blood collected from patient J. Q. on post-immunization days 0, 15, and 60. Infection with HPV-77 is not associated with a complement fixing antibody response.[10] Absence of complement fixing antibody response in J. Q. provided further evidence that he was infected with the HPV-77 virus and not with a wild rubella strain.

Conclusions

These data represent the first documentation of viremia with rubella virus after receipt of HPV-77 vaccine. However, the frequent presence of HPV-77 virus in low titers in the pharynges of vaccine recipients[5] can be explained only by the regular occurrence of viremia after the subcutaneous administration of this material. As other reported attempts to isolate HPV-77 virus from whole blood of recipients have been negative,[5,9] the viremia must be quite transient or intermittent or ordinarily of lower grade than in patient J. Q.

ADDENDUM

Since submission of this paper for publication, five other blood isolates have been obtained in a subsequent study group from two recipients of an HPV-77 derived (HPV-80) vaccine. These isolates were recovered from heparinized whole blood collected on days 11, 12 and 13 post vaccination.

These data further substantiate the occurrence of viremia after sub-cutaneous administration of these rubella vaccines.

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A SMALL BRONCHOSCOPE INSTEAD OF A LARYNGOSCOPE

"We occasionally see patients with either temperomandibular arthritis or with oral anatomic structure such that one cannot use a laryngoscope; and yet one is trying to get an endotracheal tube in. . . . The answer lies in the use of a small bronchoscope on which the endotracheal tube is mounted. An infant bronchoscope is enough to give you direct vision, is enough to give you a temporary airway, and the space required is therefore no larger than the endotracheal tube itself. This is only occasionally used, but I think it's a very handy piece of information to have. Anyone who has a small bronchoscope around can improvise."

—GABRIEL F. TUCKER, M. D., Philadelphia
Extracted from *Audio-Digest Otorhinolaryngology,* Vol. 1, No. 5, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

CASE REPORTS

Cyanosis After Closure Of Atrial Septal Defect

HENRY T. LEW, M.D., AND
ERIK CARLSSON, M.D., *San Francisco*

ARTERIAL DESATURATION MAY occur when pulmonary hypertension or pulmonic stenosis complicates an atrial septal defect. In uncomplicated atrial septal defect, abnormal position of one of the venae cavae may cause venoarterial shunting, streaming caval blood into the left atrium.[1]

Cyanosis subsequent to surgical correction of an atrial septal defect is unusual. We have had the opportunity to diagnose and study a young woman whose presenting symptoms were cyanosis and clubbing ten years after repair of a defect of the ostium secundum. The cyanosis was explained by the inadvertent diversion of the inferior vena cava into the left atrium. The importance of selective dye-dilution studies and cineangiography in establishing the diagnosis will be emphasized, although awareness of this surgical complication is the prime factor in the diagnosis.

Report of a Case

A 19-year-old woman was referred for cardiac evaluation. She was the product of a normal full-term delivery. The patient stated that a heart murmur had been present since birth. She had had frequent childhood respiratory infections and occasional cyanosis on exertion. At six years of age, a defect of the atrial septum was diagnosed by cardiac catheterization and a 10 to 15 mm gradient across the pulmonic valve was reported. At the age of nine years she was evaluated for corrective cardiac operation. On examination at that time a normal first heart sound and a well-split second sound were reported. There was an apical third sound followed by a mid-diastolic rumble and a systolic blowing murmur maximal at the left second intercostal space. No cyanosis or clubbing was present. An electrocardiogram was consistent with right axis deviation, incomplete right bundle-branch block and right ventricular hypertrophy. Roentgenographic and fluoroscopic examination of the chest showed that the heart was moderately enlarged with right ventricular predominance and increased pulmonary vasculature. On repetition of cardiac catheterization, there was a moderately large left-to-right shunt at the atrial level, but right-to-left shunting at rest or on exercise was absent (Table 1).

At operation, a large defect in the lower portion of the ostium secundum and a right pulmonary vein entering the right atrium were reportedly

TABLE 1.—*Cardiac catheterization data before and after surgical repair of atrial septal defect*

	Before Closure of Atrial Septal Defect	*Ten Years After Closure*
Hematocrit	—	49 %
Sa O_2	97.8 %	84 %
SVC O_2	—	15 vol %
RAP	6 mm Hg	4 mm Hg
RA O_2	16 vol %	14.5 vol %
PAP	21 mm Hg	13 mm Hg
PCP	9 mm Hg	—
LAP	—	13 mm Hg
LA O_2	—	19.0 vol %
QP	10.8 liters/min	6.6 liters/min
QS	3 liters/min	7.6 liters/min
R-L shunt	—	1 liters/min
L-R shunt	5.5 liters/min	—

Sa O_2: Arterial oxygen saturation. SVC O_2: Superior vena caval oxygen content. RAP: Right atrial pressure. RA O_2: Right atrial oxygen content. PAP: Pulmonary artery pressure. PCP: Pulmonary capillary wedge pressure. LAP: Left atrial pressure. LA O_2: Left atrial oxygen content. QP: Pulmonary blood flow. QS: Systemic blood flow. R-L: Right-to-left. L-R: Left-to-right.

From the Departments of Medicine and Radiology and the Cardiovascular Research Institute, University of California School of Medicine, San Francisco.

At the time of this study, Dr. Lew was a Trainee in clinical cardiology, Department of Medicine, University of California School of Medicine, San Francisco.

This investigation was supported in part by United States Public Health Service Grant Numbers HE 06285 and HE 05740.

Submitted 16 August 1968.

Reprint requests to: Department of Radiology, University of California, San Francisco Medical Center, San Francisco 94122 (Dr. Carlsson).

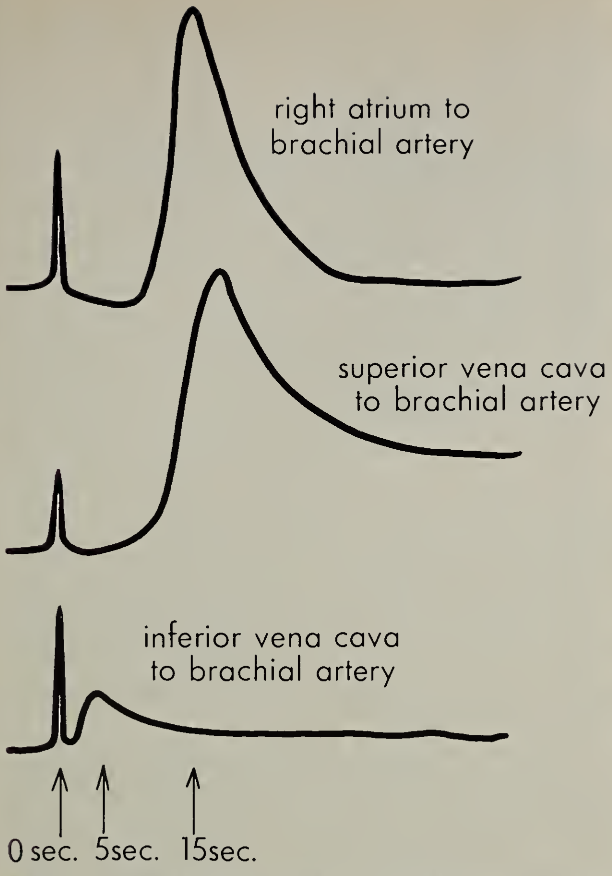

Figure 1.—Dye-dilution curves. Indocyanine green was injected into the superior vena cava, right atrium and inferior vena cava. The dye curves show the early appearance of dye from the inferior vena caval injection.

noted. Closure of the defect and transposition of a right anomalous pulmonary vein into the left atrium were performed under total cardiopulmonary by-pass (13 minutes).

The results of a follow-up examination six months later were reportedly unremarkable except for a grade I systolic murmur at the second left intercostal space.

The patient was seen for the first time at this medical center in January 1967, ten years after her operation. She complained of easy fatigue, slight exertional dyspnea, and blue fingernails and lips, present since the operation. The striking physical findings were cyanosis and clubbing of fingers and toes, which increased on exercise. The heart was not enlarged; the pulmonic component of the second sound was louder than the aortic; a faint systolic murmur was present at the base. An electrocardiogram was interpreted as normal. A roentgenogram of the chest showed a normal sized heart and normal lung fields.

Cardiac catheterization demonstrated a right-to-left shunt at the level of the inferior vena cava, but not at the atrial or superior vena caval level (Table 1, Figure 1). Arterial desaturation was present. The anatomic diagnosis was made by cineangiography, which showed contrast medium injected into the inferior vena cava entering the left atrium directly. A small amount of contrast medium passed from the inferior vena cava to the right atrium. A small defect of the atrial septum was present (Figure 2).

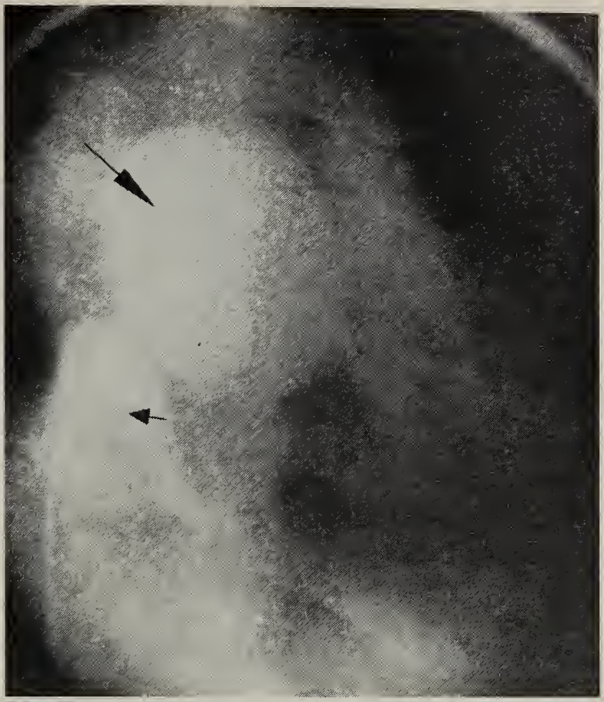

Figure 2.—As shown by the selective angiogram, the inferior vena cava (short arrow) communicates directly with the left atrium (long arrow).

At operation a midsternal opening was made and the inferior vena cava was rerouted into the right atrium. The findings were those of a small, residual low atrial septal defect through which small amounts of blood from the inferior vena cava were reaching the right atrium. The main flow from the inferior vena cava was directed entirely into the left atrium.

On follow-up examination, no cyanosis or clubbing was seen. The results of the cardiac examination were unremarkable. The patient felt well.

Discussion

Although the incidence of diversion of the inferior vena cava into the left atrium as a complication of operations to correct atrial septal defect is not known, it has been previously recognized.[2-4] The cyanosis has been detected at the time of

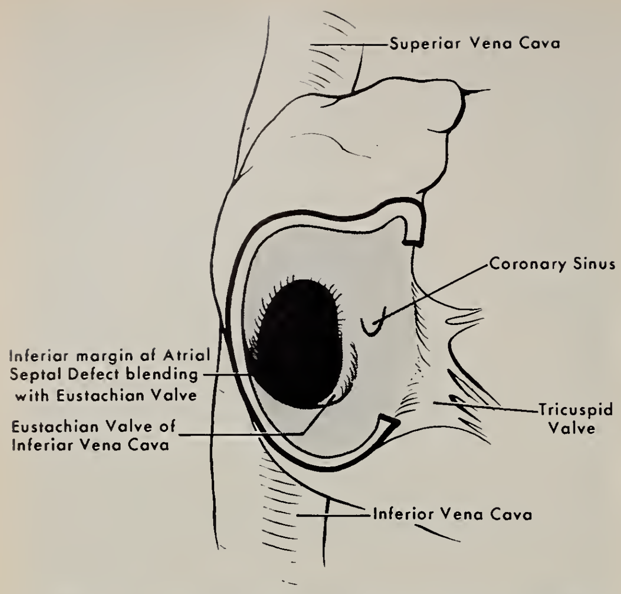
Superior Vena Cava
Coronary Sinus
Inferior margin of Atrial Septal Defect blending with Eustachian Valve
Eustachian Valve of Inferior Vena Cava
Tricuspid Valve
Inferior Vena Cava

Figure 3.—Illustration of the close relationship between low atrial septal defects and the eustachian valve of the inferior vena cava.

operation or during the postoperative period. It is possible, however, that reluctance to report such complications has contributed to a limited appreciation of this entity. As a result, cyanosis after a surgical procedure may be overlooked. The patient in the present case, who was originally operated upon at another hospital, probably had had venoarterial shunting for ten years. Some patients may not notice cyanosis except on exertion or during a respiratory tract infection,[4] and clubbing may also go undetected. The benign course of this patient is in contrast to that reported by Björk and associates, who stated that most of these patients have died.[3] The mechanism of death is not apparent.

Lack of awareness of this anatomic derangement may lead to incorrect diagnosis, even after cardiac catheterization and angiography. Staple, Ferguson and Parker[5] reported a case in which catheterization and angiography of the right heart through the superior vena cava did not result in a diagnosis. The study, repeated nine months later via the saphenous vein, was diagnostic. Conversely, if the diversion is from the superior vena cava to the left atrium, cardiac catheterization and angiography from the femoral or saphenous veins will be inadequate.

Dye-dilution studies, therefore, should be performed selectively in the superior and inferior venae cavae to demonstrate the level of right-to-left shunting. The appropriate angiographic injection will then delineate the anatomic abnormality.

Several factors contribute to the surgical error. In the case herein reported, the inferior vena cava was most probably diverted under the impression that the caval orifice was an anomalous pulmonary vein. At the time of the second operation, an anomalous pulmonary vein could not be identified. Associated with diversion of anomalous pulmonary veins has been diversion of the superior or inferior venae cavae into the left atrium.[4] Although the patient in the present case was originally operated upon during cardiopulmonary by-pass, it is probable that in cases in which by-pass was not used, lack of time to explore the atrium was a factor in the surgical error.[2] Another possibility is that the eustachian valve of the inferior vena cava may be mistaken for the inferior margin of the septal defect and be sutured in the closure. This situation is likely to arise when the defect merges with the inferior vena cava (Figure 3).

Patients with large right-to-left shunts should be operated upon again to correct the diversion. Smaller shunts in asymptomatic patients should also be corrected because of the risk of paradoxic embolism. Reoperation should entail only a low risk; several deaths, however, have been reported.[2,4]

Summary

Cyanosis and clubbing were detected ten years after an ostium secundum defect had been closed during cardiopulmonary by-pass. Cardiac catheterization and angiocardiography showed that these changes resulted from a diversion of the inferior vena cava into the left atrium. Rerouting of the flow of the inferior vena cava to the right atrium effected prompt clinical improvement.

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Current Concepts of Hyperuricemia and Gout

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■ *Recent studies have confirmed that gout is an inborn error of metabolism. It has now become evident that the hyperuricemia associated with gout might occur either due to overproduction of uric acid, underexcretion of uric acid or a combination of these processes. Furthermore, patients with excessive purine synthesis may have a specific enzyme defect resulting in altered feedback inhibition of purine synthesis. A neurological disease manifest by mental retardation, choreo-athetosis, aggressive behavior, lip-biting and self-mutilation and associated with decidedly increased purine biosynthesis serves as a prototype of this kind of disorder. Other defects in regulation of purine biosynthesis have been postulated but their existence not yet confirmed.*

It has been demonstrated that urate crystals which are deposited from hyperuricemic body fluids set up an acute inflammatory reaction by means of a variety of chemical mediators. Thus, acute gouty arthritis is now recognized as an example of "crystal induced" synovitis.

The treatment of gout consists of (1) the control of acute gouty attacks, and (2) the maintenance of normal serum uric acid concentrations. This latter may be achieved either with uricosuric drugs or with xanthine oxidase inhibition. With these principles in mind, it is now possible to avoid many of the severe crippling effects of gout and to restore the vast majority of gouty patients to useful and productive lives.

ALTHOUGH THE FIRST clinical description of gouty arthritis is attributed to Hippocrates, it has been only during the past decade that concepts regarding the pathogenesis of hyperuricemia and its relationship to gout have been firmly established. Scheele in 1776 isolated uric acid from a urinary calculus and in 1797 Wollaston demonstrated that gouty tophi contain uric acid. Garrod, in 1876, using crude methods, demonstrated that the blood of gouty patients contained excessive quantities of uric acid and subsequently it was shown that hyperuricemia was also present in the normal relatives of gouty patients. The younger Garrod in 1931[1] classified gout as "an inborn error of metabolism" but noted that no enzyme deficiency characteristic of this disease had been found. During the past

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This work partially supported by U.S.P.H.S. Grant #GM15759.

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decade, however, investigators have provided evidence for a variety of biochemical and physical abnormalities that result in hyperuricemia. Furthermore, experimental findings during this period have also provided a framework for the construction of an hypothesis for the mechanisms of the crystal induced synovitis of acute gout. These recent developments and concepts will be reviewed.

Biochemistry of Uric Acid

Properties of Uric Acid

Uric acid (2, 6, 8 trioxypurine) is weakly acidic due to ionization of the hydrogen atoms at position 9 (pKa=5.75) and 3 (pKa=10.3) while the hydrogen atoms at positions 1 and 7 do not ionize significantly. Thus at physiologic pH (7.4) uric acid exists almost entirely in the salt form as a monovalent urate ion.[2] Therefore urate is deposited in tophi as monosodium urate monohydrate[3] while due to the more acidic nature of urine, renal calculi are in the form of undissociated uric acid. Uric acid readily forms supersaturated solutions both in plasma and protein free buffer systems.[4] This phenomenon greatly hampers the ability to accurately determine solubility of urate in biological fluids.

Uric Acid Assay

The colorimetric assays for urate frequently used in routine clinical laboratories depend upon the ability of urate to reduce a reagent such as phosphotungstic acid to a chromagen.[5] Since non-urate metabolites of methylated purines (for example, caffeine or theophylline) and the other oxypurines (that is, hypoxanthine and xanthine) also reduce phosphotungstic acid, the use of colorimetric assays may give spuriously elevated values in patients ingesting caffeinated beverages, theophylline drugs or the xanthine oxidase inhibitor allopurinol. Another error inherent in colorimetric procedures for measuring uric acid results from the need to deproteinize serum with the consequent coprecipitation of some uric acid.

An enzymatic spectrophotometric method for measuring urate concentration[6] eliminates these errors. Uric acid may be measured directly in whole serum by determining the absorbancy at 292 mu at pH 9.4 before and after reaction with the highly specific enzyme uricase which is capable of converting all the uric acid present to allantoin and CO_2. This technique is sufficiently sensitive to detect microgram quantities of urate with an accuracy of 2 percent. A modification of this method for the determination of total oxypurines in urine and plasma[7] has recently been described.

During the past few years multichannel autoanalyzers have been adapted to determine serum urate by colorimetric techniques,[8] thus allowing hundreds of determinations to be performed daily with a high degree of accuracy. Because such multiphasic screening programs are in use in our hospitals and clinics today, a great number of patients with unsuspected hyperuricemia are being detected. The significance of such hyperuricemia and an approach to this problem will be discussed subsequently.

Purine Metabolism

Uric acid is truly the end product of purine metabolism in man since through the process of evolution there has been loss of the enzyme uricase which is capable of catalyzing the further metabolism of uric acid to allantoin and CO_2. Hyperuricemia, therefore may result from either increased absorption of precursor purines, increased production, decreased excretion or decreased breakdown of uric acid or from some combination of these mechanisms.

Since a purine-free diet results in an average reduction of serum urate of only 1 mg per 100 ml[9] in gouty subjects and does not correct hyperuricemia, it is clear that the hyperuricemia of gout cannot be attributed to abnormal absorption of precursor purines. It is likely, however, that an increased purine load may serve as a mechanism for the secondary hyperuricemia seen in patients with lymphoproliferative disorders with a rapid turnover of tumor cells[10] or with psoriasis where there is a rapid turnover of the skin.[11]

Uricolysis in man occurs almost entirely by action of intestinal flora upon uric acid entering the gastrointestinal tract.[12] There is no evidence that uricolysis is diminished in patients with gout and, in fact, Sorenson[13] has demonstrated that in gouty patients with reduced renal excretion of uric acid, extra-renal disposal may constitute the chief excretory mechanism for uric acid. There is, however, considerable evidence that both increased production of uric acid and reduced renal excretion of uric acid play important roles in the pathogenesis of hyperuricemia, both in primary gout and in hyperuricemia secondary to other causes.

Increased Production of Uric Acid Associated with Gout

Evaluation of Uric Acid Synthesis

Uric acid is the end-product of purine metabolism. Therefore, in the steady state when urate is not being deposited or mobilized, urate production is approximately equal to uric acid excretion. Under the standard basal conditions of a purine-free diet and no medications, the consistent daily urinary excretion of more than 600 mg of uric acid therefore is a good indication that a patient has increased uric acid production. Approximately 25 percent of gouty patients show such an excess in urinary uric acid excretion. This indirect measurement, however, does not adequately reflect uric acid synthesis in patients with impaired renal function. Uric acid production may be directly assessed by measuring the incorporation of isotopically labelled glycine into urinary uric acid and correcting such data for the disposition of the body urate pool as determined by simultaneous administration of isotopically labelled uric acid. By these techniques Seegmiller and coworkers[9] found that 67 percent of patients with primary gout had increased uric acid synthesis. Furthermore careful evaluation of studies using isotopically labeled compounds has supplied experimental evidence suggesting that among gouty patients there is no single metabolic defect in purine metabolism to account for the hyperuricemia.[2]

Control of Purine Biosynthesis

It has long been proposed that among gouty patients who overproduce uric acid there may be a defect in the feedback control of purine biosynthesis.[2] Feedback control of purine biosynthesis would be expected to be exerted on the first irreversible step of purine biosynthesis—that is, the enzymatic reaction of glutamine with 5 phosphoribosyl-1-pyrophosphate (PRPP) to form 5 phosphoribosylamine (Chart 1). Suppression of purine biosynthesis by the addition of preformed purines either as free bases or ribonucleotides has been demonstrated in cultured mammalian cells,[14,15] bacterial systems[16] and in liver slices.[17,18] An increased rate of purine biosynthesis thus could result from a loss of the sensitivity of the rate controlling enzymes to feedback inhibitors, from a diminished concentration of the normal end products that function as feedback inhibitors, or from an increase in concentration of one of the substrates available for the rate limiting reaction.

The first evidence of a regulatory mechanism for control of purine biosynthesis in man came from studies using the purine precursor 4-amino-5-imidazole carboxamide (AIC). Administration of this compound to non-gouty subjects substantially reduced *de novo* uric acid synthesis.[19] Subsequently the drug 6-diazo-5-oxy-1-norleucine (DON) was also shown to suppress purine biosynthesis in gouty subjects.[20] Toxic side effects, however, have precluded the clinical use of these compounds.

Recently there have been exciting new developments in this area. In 1966 Sorenson[21] found that administration of the purine analog azathioprine (Imuran®) to three gouty patients inhibited their excessive purine synthesis, as measured by a decrease in the uric acid content of plasma and urine as well as the glycine-1-C^{14} incorporation into urinary uric acid. Two normal subjects and one gout patient who produced normal quantities of uric acid showed no significant suppression of urate production in response to azathioprine treatment. Sorenson therefore proposed that azathioprine produced a unique effect in gouty patients who were overproducers of uric acid, thus implying that the regulation of purine synthesis may differ in different types of gout.

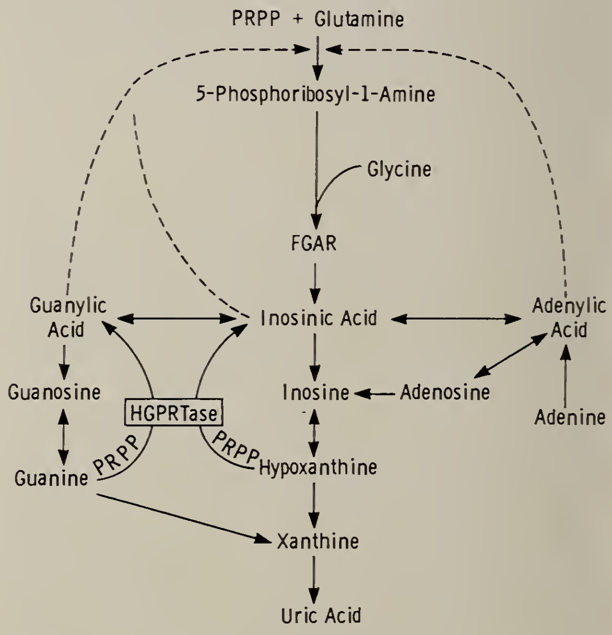
Lesch and Nyhan in 1964 at the Johns Hopkins Hospital first described a familial neurological disorder consisting of choreoathetosis, spasticity, mental retardation, aggressive behavior and compulsive biting resulting in mutilation of the lips and fingers.[22] These findings in two young brothers were associated with hyperuricemia, urinary uric acid excretion which was three to six times normal and incorporation of from 100 to 200 times the normal amount of glycine-1-C^{14} into urinary uric acid. Numerous other cases have subsequently been described, limited to males and with a striking familial distribution compatible with x-linked inheritance.[23] Although the degree of overproduction of uric acid found in children with the Lesch-Nyhan syndrome was greatly in excess of that encountered in adults with clinical gout, gouty arthritis has remained a relatively late occurrence in these children. Gouty nephropathy, however, was a contributing factor to the death of some of these patients in early puberty.[24]

Because of the pronounced excess of uric acid produced by these children, Seegmiller and coworkers[25] compared the effect of azathioprine in two children with Lesch-Nyhan syndrome and two gouty men who were also overproducers of uric acid. They found that azathioprine suppressed purine synthesis in the two gout patients but did not diminish it in the children. Since the pharmacologic action of azathioprine probably results from its degradation to 6-mercaptopurine (6MP) the effect of 6MP on the purine synthesis of fibroblasts grown *in vitro* from biopsy specimens of skin obtained from a child with the Lesch-Nyhan syndrome was compared with its effect on cells grown from normal subjects. It was found that 6MP greatly inhibited purine biosynthesis in normal cells but had no effect on cells derived from the child with the neurological disorder. Resistance to the action of 6MP had previously been described in mutant mammalian tumor cells[26] and leukemic leukocytes,[27] and this phenomenon was ascribed to a deficiency of the enzyme hypoxanthine-guanine phosphoribosyl transferase (HGPRTase). Therefore, Seegmiller examined the activity of this enzyme in the fibroblasts grown *in vitro* as well as in hemolysates of washed erythrocytes and found that the enzyme activity from cells of affected children was less than 0.05 percent of normal.[25]

It was thus enticing to attempt to explain both the neurological disease and the increased purine synthesis on the basis of this enzyme defect. Rosenbloom and coworkers[28] demonstrated HGPRTase deficiency in the brain and liver as well as fibroblasts and erythrocytes of these affected children. They noted that the absence of this enzyme activity in the basal ganglia where it is normally of highest activity could be correlated with the fact that the major clinical symptoms are attributable to basal ganglia dysfunction. It was also observed that the concentration of oxypurines in the cerebrospinal fluid (CSF) was four times normal and was greater than in the plasma, thus suggesting that the brain also had an increase in purine synthesis. No detectable increase in CSF uric acid concentration was noted. Thus the neurological dysfunction could be secondary to increased concentration of oxypurines or other metabolites of enhanced purine biosynthesis or possibly due to a failure to maintain adequate intracellular concentration of certain purine nucleotides necessary for normal brain function.

The existence of a causal relationship between the deficiency in HGPRTase and accelerated purine biosynthesis is suggested by the following evidence: (a) there is an inverse relationship between the degree of enzyme deficiency and the rate of purine biosynthesis,[25,29] (b) both the enzyme deficiency and either the neurological disease of children or the gouty arthritis in appropriate kindreds are inherited in an x-linked manner,[23,30] (c) all patents with HGPRTase deficiency to date have been shown to have accelarated purine biosynthesis.

This relationship between HGPRTase deficiency and accelerated purine biosynthesis was studied in detail, using fibroblast cultures.[31] Lack of HGPRTase had no detrimental effect on the rate of growth of the fibroblasts. The enzyme deficient fibroblasts had accelerated rates of purine biosynthesis and elevated levels of PRPP, although the rate of synthesis of this compound was not increased. These cells were sensitive to feedback inhibition of purine synthesis by nucleotides of adenine and 6 methylmercaptopurine ribonucleoside but the rate of purine synthesis was increased rather than decreased by hypoxanthine and guanine. Based on these studies it was concluded that the acceleration of purine biosynthesis is probably due to an increase in the activity of phosphoribosyl pyrophosphate glutamine amidotransferase, the enzyme catalyzing the first irreversible step of purine biosynthesis (Chart 1).



PRPP . . . .phosphoribosyl pyrophosphate
FGAR . . . .formyl glycinamide ribonucleotide
HGPRTase . .hypoxanthine - guanine phosphoribosyltransferase
– – – indicates inhibition

Chart 1.—Pathways of purine metabolism. The first irreversible step of purine biosynthesis, PRPP + glutamine, is catalyzed by phosphoribosyl pyrophosphate glutamine amidotransferase.

Abnormalities of Purine Biosynthesis In Patients with Gout

In addition to the complete deficiency of HGPRTase described in patients with the Lesch-Nyhan syndrome, Kelly and coworkers described a partial deficiency of this enzyme in five affected members of two families with gout.[29,32] Ten other gouty patients with excessive purine biosynthesis similarly studied had normal concentrations of this enzyme.[29] These patients with gout and a partial enzyme deficiency not only had some residual enzyme activity but also showed different amounts of activity depending upon whether hypoxanthine or guanine served as the substrate, suggesting that the HGPRTase which is present in these patients may be structurally different from both the normal enzyme and from other affected patients. Other instances of partial deficiencies of HGPRTase in patients with gout and minimal neurological abnormality have been reported[33] including a 21-year-old man who had onset of gout at age 15 and has very low residual HGPRTase activity but nevertheless has only a minimal neurological deficit and had no evidence of self-mutilation.[34]

The demonstration of an enzyme defect in patients with primary gout and excessive purine synthesis has indeed confirmed Garrod's original proposal that gout is "an inborn error of metabolism."[1] Furthermore it affords a possible explanation as to why these patients have excessive purine biosynthesis[35] and abnormal resistance to the suppressive effects of azathioprine[36] and allopurinol[37] on purine production. However, this single enzyme defect occurs in less than 30 percent of patients with primary gout and excessive purine synthesis and therefore different metabolic defects are probably present in these other patients. Rosenbloom and coworkers[38] recently demonstrated decreased sensitivity to feedback inhibition of purine biosynthesis in cultured fibroblasts from two patients with increased purine production and normal HGPRTase concentrations. They suggested that the first enzyme of the *de novo* purine pathway, 5-phosphoribosyl-1-pyrophosphate glutamine amidotransferase (Chart 1), may be abnormal in the gouty patients and thus less sensitive to feedback inhibition.[39] However, Seegmiller and coworkers,[40] studying similar patients, found normal suppression of glycine-1-C^{14} incorporation into urinary uric acid following adenine administration, thus suggesting that feedback inhibition is intact. These investigations all provide additional evidence for heterogeneity of the causes of hyperuricemia, even in patients with gout and excessive purine biosynthesis and suggest that only within given families may common causes for hyperuricemia be found. Numerous investigations are under way in an attempt to delineate additional specific defects in purine metabolism in patients with increased uric acid production.

Renal Excretion of Uric Acid

A diminished renal excretion of uric acid in gouty patients was suggested as a possible cause of hyperuricemia nearly a century ago. Gutman and Yü[41] failed to show significant differences in the urate/inulin clearance ratios between normal and gouty subjects. Nugent and Tyler,[42] however, showed that six gouty subjects had urate/inulin clearance ratios significantly lower than those of normal subjects made comparably hyperuricemic with a high purine diet. This finding was confirmed by Seegmiller and coworkers,[43] who found a diminished urate/inulin clearance ratio in all five gouty subjects who showed normal uric acid production, while among patients who produced excessive amounts of uric acid the urate/inulin clearance ratios were identical with those of normal control subjects in whom hyperuricemia was induced by dietary means. Other gouty patients showed some degree of both overproduction and diminished renal excretion of uric acid, again suggesting the heterogeneity of causes for hyperuricemia among gouty patients. Diminution in renal clearance of uric acid may be produced by a variety of chemical substances and drugs. It may account for the hyperuricemia seen after the ingestion of low doses of salicylates,[44] chlorothiazides[45,46] or an association with the lactic acidemia of glycogen storage disease[47] or the ketoacidosis of diabetes mellitus or starvation.[48]

The mechanism for the excretion of uric acid by the kidney was originally thought to consist of complete filtration of uric acid at the glomerulus followed by tubular reabsorption of 90 to 95 percent of the filtered load[41] without appreciable tubular secretion. However, evidence for tubular secretion of uric acid now includes: (a) studies of a patient with hypouricemia in whom urate/inulin clearance ratios exceed 1:1,[49] (b) induction of clearance ratios of urate to insulin greater than 1:1 by administration of uricosuric drugs during mannitol diuresis,[50] (c) the paradoxical effects of salicylates which causes urate retention when given in low doses (attributed to inhibition of tubular secretion) and uricosuria when given at high doses (attributed to inhibition of tubular reabsorption).[44]

Tubular secretion has also been shown to play a role in the renal excretion of the oxypurines (hypoxanthine and xanthine).[51] Although the exact sites of tubular secretion have not been elucidated there is at least some indirect evidence for competition between uric acid and oxypurines for renal tubular secretion.[51,52]

Thus, it is currently believed that uric acid is filtered at the glomerulus, and that the filtered uric acid is completely reabsorbed in the proximal tubules and that excreted uric acid is the result almost entirely of a tubular secretory process. This concept presumes that urate is entirely filterable and therefore not bound to protein. Evidence suggesting that there may, in fact, be some binding of urate to proteins, as discussed below, may necessitate additional alterations in our concept of the mechanisms of renal excretion of uric acid.

Acute Gouty Arthritis

The Inflammatory Reaction

Recent concepts of the mechanisms responsible for attacks of acute gouty arthritis really represent rediscoveries of early hypotheses proposed by Garrod,[53] Freudweiler[54] and Roberts.[55] Garrod considered acute gouty arthritis to be an inflammatory reaction to crystals of sodium urate deposited from hyperuricemic body fluids in and about the joints during an acute attack. However, evidence against Garrod's proposals included: (a) the reported failure of injected urate to give rise to an inflammatory response, (b) the generally painless nature of tophi which were shown to be deposits of urate crystals, (c) the poor correlation between acute attacks of gout and the serum urate concentration, and (d) the paradox whereby colchicine, which has a remarkable therapeutic effect on acute gouty arthritis, does not alter the serum urate concentration while uricosuric agents, which lower the serum urate may, in fact, trigger acute gouty attacks. Therefore this hypothesis was abandoned, even after Roberts in 1892[55] found that synovial fluid obtained from patients with acute gouty arthritis was "laden with crystals of sodium biurate."

The above concepts were reassessed beginning in 1961 when McCarty and Hollander[56] again identified urate crystals in gouty synovial fluid. Additional evidence was obtained when Seegmiller and coworkers[57] showed that intra-articular injections of microcrystalline monosodium urate monohydrate in gouty and non-gouty volunteers produced warmth, swelling and pain indistinguishable from the signs and symptoms of acute gout. Similar injections of an amorphous urate suspension produced little reaction. Independently, Faires and McCarty[58] confirmed this work and also produced synovitis in dogs with intra-articular urate injections.

Based on these experimental findings, Seegmiller and Howell[59] proposed the following mechanism for the development of acute gouty arthritis: (a) there is intra-articular deposition of microcrystalline monosodium urate monohydrate from hyperuricemic body fluids, (b) there develops an acute inflammatory reaction to the crystals with local infiltration, predominately by granulocytes, which phagocytize the urate crystals, (c) propagation of the acute inflammatory reaction by continued introduction of new crystals possibly due in part to alterations in local factors (such as decreasing pH) with further decrease in urate solubility.

Urate Deposition

A key point in this hypothesis is the deposition of urate crystals from hyperuricemic body fluids and therefore there has been considerable interest in factors that might be responsible for urate deposition. Since physical chemical properties are of great importance we studied the solubility of uric acid and sodium urate in serum.[4] When uric acid rather than sodium urate is incubated with serum for one hour and the excess crystals then removed by passing the serum through a millipore filter of 0.22 mu, it was found that a urate concentration in the filtrate of approximately 400 mg per 100 ml could be achieved. Immediately after filtration there was spontaneous crystallization of monosodium urate monohydrate from the supersaturated solution. Concentrations of urate in solution diminished rapidly at first and then more slowly, reaching an ultimate concentration of 8.5 mg per 100 ml after about three days' incubation. With lower concentrations of uric acid in the serum there was greater stability of these supersaturated solutions such that at urate concentrations of approximately 50 mg per 100 ml the solutions would be stable for as long as four days without evidence of spontaneous crystal formation. Only when crystals of sodium urate were added to seed the system was there precipitation. Therefore we explored the possibility that sodium urate may exist in supersaturated solutions in the range of serum urate concentrations commonly encountered in clinical practice. Serum obtained from gouty and non-gouty subjects was incubated with crystals of monosodium urate. After two hours' incubation the crystals were filtered off and the concentration of urate in the solution was determined. At initial serum urate values of less than 7 mg per 100 ml, sodium urate went into solution, while at initial values greater than this, urate precipitated from solution during the incubation period. This provided an *in vitro* model of the deposition of tophaceous deposits at high serum urate levels and the resolution at low serum urate concentrations. It further illustrated the central importance of bringing the serum urate concentration of a gouty patient into the normal range for effective management of their disease. It also allowed some speculation that one of the essential differences between the gouty patient and his equally hyperuricemic brother could be the chance formation of the first crystal of sodium urate.

Urate Binding to Plasma Proteins

In addition to the primarily physical chemical considerations there has also been increasing interest that other factors might be responsible for increased uric acid deposition seen in patients with gouty arthritis. It has been noted, for example, that in certain conditions associated with extremely high serum urate concentrations, such as lymphoproliferative disorders and chronic renal disease, acute gouty attacks are infrequent, while patients with primary gout have only modest elevations of the serum urate. This might then suggest other factors, peculiar to patients with gout, that would afford an increased propensity to urate deposition. One prime possibility is that urate in biological fluids exists in combination with other substances which might help to solubilize the urate.

The possibility that urate is bound to plasma proteins has been extensively investigated in the past with conflicting results. Recently, however, Alvsaker, using the methods of gel filtration and immunoelectrophoresis followed by autoradiography, demonstrated a reversible interaction between urate and albumin,[60] low density beta lipoprotein, beta 2-macroglobulin and an alpha 1-alpha 2 globulin.[61] Furthermore, he noted the absence of this alpha 1-alpha 2 globulin in seven out of eight patients with primary gout. He therefore concluded that the alpha 1-alpha 2 globulin serves as a specific transport protein for uric acid in blood, is absent in patients with primary gout, and is in some way associated with the pathogenesis of this disease. Subsequently, Alvsaker noted that low concentrations of this urate-binding protein are present in gouty patients and has suggested genetic control over the concentrations of this protein.[62] Using the method of equilibrium dialysis, we have been able to confirm a decreased binding of uric acid to plasma proteins in three patients with severe tophaceous gout.[63] We have found normal uric acid binding in plasma from patients with non-tophaceous gout, asymptomatic hyperuricemia, and secondary hyperuricemia. Urate binding to plasma proteins was also significantly decreased by salicylates. Effects of other drugs on this phenomenon are being investigated. Katz and Ehrlich[64] recently isolated from serum an acid mucopolysaccharide which may be bound to alpha or beta globulin and which has the ability to significantly increase the solubility of urate and to prevent uric acid crystallization. The possible significance of this substance in the pathogenesis of acute gout has not yet been determined.

Chemical Mediators of Inflammation

According to the unitary concept of gout previously described, deposition of crystals of sodium urate are involved, not only in tophaceous aspects of the disease, but also in the pathogenesis of the acute gouty attack. A possible relation between urate crystal deposition and chemical mediators of inflammation has therefore been intensively evaluated. During the past few years, there has been considerable evidence that a group of vasoactive polypeptides called kinins are mediators of a wide variety of inflammatory reactions. Melmon and coworkers[65] demonstrated that very small quantities of purified bradykinin injected intraarticularly in dogs produced signs of inflammation within 20 minutes. This effect could be completely abolished by injection of carboxypeptidase, an enzyme capable of destroying bradykinin, immediately after the bradykinin injection. Significantly elevated kinin concentrations were also found in synovial fluid obtained from the knee joints of patients with spontaneous gouty arthritis, synovitis induced by injection of microcrystalline sodium urate and patients with other types of acute inflammatory synovitis. Thus, it has been concluded that kinins may be mediators of some of the inflammatory synovial reactions, not only in gouty arthritis, but in some other forms of arthritis as well.

Kellermeyer[66] showed that Hageman factor, a plasma protein which serves as the initial component of the intrinsic blood clotting mechanism, as well as the initiator of a series of reactions relating to mediation of inflammation, is activated by urate crystals. He therefore proposed that when a sufficient number of urate crystals are present within the joint space, Hageman factor is activated to a level adequate to initiate the formation of inflammatory mediators — that is, permeability factor, kallikrein, and kinin-like substances. These inflammatory mediators increase capillary permeability and induce margination of leukocytes along venular walls and emigration into the synovial space. The leukocytes then phagocytize the urate crystals. During the process of phagocytosis, the leukocytes may enhance the inflammatory response by producing additional inflammatory mediators. On this basis it has been proposed that there are two major components for the inflammatory mechanism of acute gouty arthritis: (a) activation of Hageman factor by urate crystals which, in turn, enhances the accumulation of leukocytes in the joint space and (b) prolongation and accentuation of the inflammatory process by the accumulated leukocytes.

The current status of the role of chemical mediators in the inflammatory reaction associated with gout has been summarized as follows[67]: Kinins are present in the synovial fluid of the inflamed gouty joint in concentrations which are biologically effective. They may be formed by an established action of monosodium urate crystals on Hageman factor and also possibly by various modes dependent on leukocytes. The finding that arthritis induced by urate crystals may develop and persist in the presence of high concentrations of kinin-destroying carboxypeptidase suggests that other pathogenetic factors are important, but it does not exclude the possibility that the kinin-forming system also plays a role. In gout, the crystals deposited in synovial tissues may induce kinin formation in the interstitial fluid where the kinins will be relatively protected from destroying enzymes and in a particularly good position to cause pain and vascular changes. Furthermore, kinin-forming enzymes and similar proteases may also attack tissues, not only through the release of kinins, but also by direct action. These actions would not be affected directly by kinin-destroying enzymes. This kinin-forming system is, then, one of the mechanisms through which urate and other microcrystals might produce synovitis. Other pathogenetic processes independent of kinin formation undoubtedly also contribute to this reaction.

The Treatment of Gout

Colchicine was first used for "rheumatism" in the 6th century A.D. but it was not until the 18th century that it was found to be quite specific for acute attacks of gouty arthritis. Nevertheless, for many centuries colchicine shared its popularity for the treatment of gout with many herbs, medical concoctions, mechanical devices, ointments, counter-irritants, acupuncture, blood-letting and galvanic current. Our new concepts regarding mechanisms of hyperuricemia and the pathophysiology of acute gouty arthritis have made it possible to consider treatment of gout on a more rational basis.

The management of a patient with gout requires from the outset that two aspects be considered independently: One is the acute attack of gouty arthritis; the other is hyperuricemia with possible tophaceous deposits, renal calculi or renal insufficiency. Clearly this point cannot be overemphasized since the approach to each is entirely different; the drugs utilized are different and therapy aimed at one phase may, in fact, exacerbate the other. Undoubtedly, the failure to understand these basic tenets caused much of the early confusion surrounding the pathogenesis of gout, since it seemed difficult to implicate an abnormality related to uric acid as the cause of gout when colchicine, the most specific therapeutic agent for gout, did not alter the serum urate concentration, and uricosuric agents which did lower the serum urate did not relieve attacks of gout and, in fact, often worsened the attacks. Our current understanding of the pathogenesis of gout has resolved these paradoxes.

Management of Acute Gouty Arthritis

Colchicine remains the most specific and most valuable drug for an acute attack of gout. For the fully developed acute attack, one tablet (0.6 mg) of colchicine should be given every hour, either until the patient experiences relief of pain or side effects such as nausea or diarrhea develop, but probably no more than 12 tablets should be given for any single attack. Colchicine may also be administered intravenously (2 mg colchicine diluted with normal saline solution to a total volume of 20 ml and injected slowly intravenously over a 5-minute period) and produce a more prompt and effective response, with fewer gastrointestinal side effects. No more than 5 mg of colchicine should be given intravenously during a 24-hour period. Patients with renal insufficiency should be given even smaller doses, for they excrete colchicine very slowly.

The mechanism of action of colchicine in patients with acute gouty arthritis is still not entirely clear. Seegmiller and coworkers proposed[68,69] that colchicine has its effect on white cell metabolism, since they demonstrated that colchicine diminished the metabolic activity of leukocytes during phagocytosis. They suggested that colchicine's action in acute gouty arthritis is mediated through interference with lactic acid production by phagocytes, thus preventing a significant pH gradient and inhibiting the reseeding of urate crystals necessary for continuation of gouty inflammation. Wallace,[70] however, using an *in vitro* system, demonstrated that trimethylcolchicine acid, an analogue of colchicine with approximately equal efficacy to the parent compound in the treatment of acute gout, has no effect on acid production by leukocytes. Thus, by inference, he argued that this cannot be the mechanism of action for colchicine. Suggested mechanisms include: That colchicine may inhibit chemotaxis of normal polymorphonuclear leukocytes[71,72]; that colchicine interferes with leukocyte migration by inhibiting ameboid motility[73]; and that colchicine interferes with the process by which phagosomes fuse with lysosomal membranes.[74,75] Although Weissmann has proposed that most anti-inflammatory drugs act by stabilization of lysosomes, there is no evidence that colchicine has any direct effect on isolated lysosomes.[76] All of these proposals may be partially correct and each could explain the effect of colchicine relative to the hypothesis for crystal induced synovitis which has been reviewed.

For patients intolerant or unresponsive to colchicine, the use of indomethacin (Indocin®) in doses of 50 mg three times daily for four to seven days is recommended. This therapy has been found to be quite effective and free from major toxicity.[77] Neither colchicine nor indomethacin have any significant effect on the serum uric acid concentration. Probenecid, however, has been shown to decrease the renal excretion of indomethacin,[78] and therefore special attention must be paid to potential toxicity when these drugs are used in combination.

Phenylbutazone (Butazolidin®) remains an effective anti-inflammatory and analgesic drug which, although not specific is still of considerable value in the management of acute gout. The dosage is 200 mg four times daily for two to three days, with gradual tapering over the next two to three days. Kuzell[79] has reported 93 percent major improvement in patients with acute gout receiving phenylbutazone. In one double blind crossover trial[80] 600 mg of phenylbutazone was found to be more effective than 100 mg of indomethacin for the treatment of acute gout. Although the toxic effects of phenylbutazone are minimal in the short term use of this agent for acute gout, potentially serious toxicity, such as bone marrow depression, forces even the staunchest advocates to advise caution in its long term use for this disorder. In addition to its anti-inflammatory properties, phenylbutazone is also a uricosuric agent, a fact which must be kept in mind whenever balance studies are being done on patients receiving this drug.

Oxyphenbutazone (Tandearil®) is a closely related compound with similar anti-inflammatory, but no uricosuric properties. It is administered in initial doses of 400 mg with maintenance of 100 mg every four hours for a period of about four days.

There is no indication for the use of systemic corticosteroids in the management of gout. ACTH is occasionally used for very severe attacks of gout when all other agents have failed or if the patient is intolerant to all other agents.

Treatment of Hyperuricemia In Patients with Gout

Despite the fact that it has been shown that the hyperuricemia associated with gout might arise from a variety of causes, it seems quite clear that the hyperuricemia of gout still provides an acceptable explanation of the development of tophaceous deposits. It is also a source of hyperuricemic body fluids from which crystals may precipitate to bring about an attack of acute gouty arthritis as discussed previously. This, in essence, is the basis for the treatment of hyperuricemia. Today, with adequate means available for diagnosing hyperuricemia in gout and with potent drugs available to decrease the serum urate concentration, there is no longer any excuse for the development of progressive tophaceous gout.

Therapy aimed at lowering the serum urate concentration is indicated in any of the following conditions: (1) presence of tophaceous deposits as noted either on physical or roentgenological examination; (2) serum urate concentration which is consistently 1 to 1.5 mg per 100 ml above normal in a patient with gouty arthritis; (3) persistence of joint symptoms despite a modest increase in the serum urate concentration.

There are now two types of therapy available to decrease the serum urate concentration; the first is uricosuric therapy which has, until recently, been the only kind of therapy available; second, a newer kind of treatment involves the use of an enzyme inhibitor to block uric acid production.

The objective of uricosuric therapy is to increase the renal excretion of uric acid and thereby reduce the serum urate concentration to normal.[81] Frequent determination of the serum urate concentration is essential, as this is the only guide to effective management. To avoid the sudden exposure of the kidney to large quantities of uric acid and to prevent precipitation of an acute attack of gouty arthritis, uricosuric drugs should be started at low doses and gradually increased over a period of seven to ten days.

Probenecid (Benemid®) has been available for clinical use since 1950, and has proved to be a very effective uricosuric agent in most patients with gout.[82,83] With 1 gm daily dosage, there is a mean increase of approximately 50 percent in the renal excretion of uric acid in gouty subjects and a mean fall of about one-third of the serum urate concentration. Because the biological half-life of probenecid in man is six to twelve hours, it is advisable to administer this drug in divided doses. Maximum recommended daily dosage is 3 gm.

In instances where toxicity occurs with probenecid, or if this drug is ineffective, then the administration of sulfinpyrazone (Anturan®) is suggested. This phenylbutazone derivative has potent uricosuric but no anti-inflammatory properties. When given to gouty subjects in daily dosage of 800 mg, it will almost double the 24-hour urinary output of uric acid, with reduction of the serum urate to about half the initial concentration.[83] Again, the dosage of the drug should be increased until the desired serum urate concentration is achieved, the maximum dosage being 800 mg daily in divided doses.

Both probenecid and sulfinpyrazone have relatively few side effects and are usually well tolerated. The most common adverse reaction is gastric intolerance, although drug fever and drug rashes are occasionally encountered. Concomitant administration of salicylates in any dosage nullifies the uricosuric effect on both of these agents. Acetaminophen (Tylenol®) has no effect on the serum urate concentration and may be used as an analgesic or antipyretic in patients with hyperuricemia even when they are taking uricosuric drugs.

Allopurinol in the Treatment of Gout

For many years it has been felt that the most rational approach to the therapy of hyperuricemia would be to inhibit uric acid production, rather than to increase urate excretion. Attempts to find such a drug, however, resulted only in substances which were too toxic for human use. Recently, however, Elion, Hitchings and their colleagues[84] investigated allopurinol (4-hydroxy pyrazolo pyrimidine) in relation to the metabolic inactivation by xanthine oxidase of 6-mercaptopurine. They noted that this potent inhibitor of xanthine oxidase, which could be given to humans without adverse effect, decidedly decreased uric acid production. This compound is structurally similar to hypoxanthine, differing only by transposition of a carbon and nitrogen in the purine ring. As a xanthine oxidase inhibitor, it prevents the conversion of hypoxanthine to xanthine and of xanthine to uric acid. Thus, these other oxypurines accumulate in the blood and are subsequently excreted. Administered in doses of 300 to 800 mg a day, allopurinol has been very well tolerated by most patients.[85] It has now been administered to thousands of patients with occasional instances of drug rashes, transient leukopenia and transient aberrations of liver function tests but few serious side effects noted. One fatal case of exfoliative dermatitis was recently reported.[86] Attacks of acute gouty arthritis are also occasionally aggravated during the early stages of treatment. This is similar to the effect of the institution of uricosuric therapy and may be prevented by starting with low dosages of allopurinol and gradually increasing the dose. Since it has been shown that the renal clearance of oxypurines is much greater than that of uric acid,[51] and the solubility of xanthine and hypoxanthine exceed that of uric acid,[85] it would appear that the inhibition of xanthine oxidase is indeed advantageous. Despite some of these apparent advantages of allopurinol, it still remains a relatively new drug and there is some concern about potential toxicity, such as development of xanthine stones in the kidneys. This is based primarily on the fact that xanthine calculi have developed in aproximately 50 percent of the patients with the metabolic defect xanthinuria, which has been shown to be due to the congenital absence of the enzyme xanthine oxidase.[87] Thus, it is generally felt that conventional uricosuric therapy is sufficient for most patients with gout and hyperuricemia and that allopurinol should be reserved for specific indications.[88] If it is demonstrated at some future time that increased renal excretion of uric acid has some deleterious effect on the kidneys, then allopurinol will have undisputed claim as the drug of choice. At present, we must weigh the benefits of this effective agent against the hazards both real and potential. The primary indications for the use of allopurinol in patients with hyperuricemia and gout include: (1) patients who respond poorly to maximal uricosuric therapy. This is most likely to occur in patients with renal impairment who cannot excrete an increased uric acid load. Allopurinol administration may afford the only means by which such patients may achieve normal serum urate concentrations. (2) Patients who have allergic sensitivity or an intolerance for uricosuric drugs. (3) Patients with demonstrated uric acid renal calculi. (4) Patients with massive tophaceous involvement. (5) Patients with hyperuricemia secondary to myeloproliferative disorders, especially before treatment with cytotoxic agents. These are the patients in whom, otherwise, acute uric acid tubular blockade might develop.

Although it has frequently been suggested that allopurinol and uricosuric drugs may be used together, it has recently been shown[52] that the combined use of these drugs is indicated only when patients have good renal function and when the aim of therapy is to unload a maximal amount of urate, as for example in patients with severe tophaceous involvement. In other situations it appears that uricosuric drugs, as well as salicylates, impair the renal excretion of oxypurines.

The use of allopurinol in patients with overproduction of uric acid and neurological deficiency has also been questioned. Since it has been shown that allopurinol does not decrease total purine synthesis in these patients[37] and since it is possible that the neurological dysfunction in patients with the Lesch-Nyhan syndrome is a result of increased concentration of oxypurines, it therefore follows that allopurinol therapy may, in fact, have a deleterious effect in such patients.[28] Recently it was reported that an infant with this syndrome was treated from four days of life with allopurinol and that such therapy was not successful in preventing the appearance of mental retardation, spasticity or self mutilation in this patient.[89]

Interval Treatment

The interval treatment of gout is concerned primarily with lowering serum urate concentration and preventing acute attacks. This therapy usually consists of the use of a uricosuric drug and prophylactic colchicine, usually in doses of 2 or 3 tablets daily.[82] As previously discussed, to be effective the uricosuric drug must be given in a sufficient dosage to lower the serum urate concentration to within the normal range. This aspect of therapy should help decrease the incidence of gouty nephropathy, as well as prevent the development of tophaceous complications. The prophylactic use of colchicine is very helpful in preventing recurrent acute attacks.[90] The only consideration currently given to diet is in the avoidance of those foods which are known to be very high in purine content. If significant hyperuricemia is a problem, it is usually better controlled with uricosuric drugs than by dietary means alone. Obviously those medications or situations known to produce hyperuricemia or provoke acute attacks of gout should be avoided in patients with known gout. This would include such drugs as thiazides and salicylates and would also include alcohol ingestion,[91] total caloric restriction[92] and physical or emotional stress.[93]

Treatment of Asymptomatic Hyperuricemia

With the increased use of multiphasic screening programs in hospitals and clinics, the incidence of unanticipated or asymptomatic hyperuricemia is continually increasing.[94] In patients with hyperuricemia associated with gout where deposition of urate either in joints or other tissues has been demonstrated it is quite clear that the lowering of the serum uric acid concentration in the blood is a rational basis for treatment. However, there is no definitive study to show the fate of untreated patients with asymptomatic hyperuricemia and therefore there are no firm guidelines as to which, if any, of these patients should be treated. There is, however, some suggestion that patients with asymptomatic hyperuricemia may have some specific types of renal tubular dysfunction[95] and therefore it is quite possible that such patients could have deterioration of renal function, possibly related to hyperuricemia even before they have clinical evidence of gout. Furthermore there is evidence that the likelihood of acute gouty arthritis increases proportionally to the serum urate concentration.[96] Thus, it has been recommended that all patients with sustained serum urate concentrations greater than 9 mg per 100 ml should be treated regardless of the cause of the hyperuricemia.[97] It is hoped that within the next decade definitive studies will be completed to answer this most important question.

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SHOCK FROM AN INFECTED CATHETER

"A patient [who] has been on IV fluids through a catheter for four or five days suddenly [and mysteriously] goes into shock; and you don't know what it's all about. Perhaps he has a little bit of fever. If you get that little tip-off, take the catheter out, and you may have a miraculous cure right then and there. No treatment will succeed that does not include early . . . removal of the infected catheter."

—Edward D. Frank, M.D., Boston

Extracted from *Audio-Digest Anesthesiology,* Vol. 10, No. 19, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

MEDICAL STAFF CONFERENCE

Choriocarcinoma

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Associate Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. BAGSHAW:* The patient is a 23-year-old Caucasian housewife who was admitted to the Cancer Research Institute 23 June 1968 for further evaluation and treatment of known choriocarcinoma.

From the time of her birth through April 1968, she was in good health. She had a normal menarche and subsequent menstrual history, and had two uncomplicated deliveries. On 22 April 1968, she delivered a 12-pound stillborn infant. The postpartum period was complicated by continued uterine bleeding. On 29 May 1968, she was admitted to a local hospital, where she received a blood transfusion because of anemia, and dilatation and curettage were performed. The pathologist's report indicated choriocarcinoma of the uterine tissue. In subsequent studies a Gravindex was positive and no abnormality was seen on an x-ray film of the chest. On 5 June 1968, a total abdominal hysterectomy was performed and the pathologist's report confirmed the diagnosis of choriocarcinoma. The Gravindex at that time was again positive, and another roentgenogram of the chest showed areas of density on both sides. On admission to the Clinical Unit of the Cancer Research Institute (23 June 1968) the past history, review of systems and family history were essentially non-contributory. The patient was well developed and appeared well nourished and in no distress. The only significant finding on physical examination was discharge of a brownish fluid from the vagina. Small nodules were noted on the anterior wall of the vagina on pelvic examination.

The significant laboratory findings at the time of admission were as follows: hematocrit, 26.2 percent; leukocytes 3,900 per cu mm, with a normal differential determination; platelets, 936,000 per cu mm. Urinalysis showed the presence of 40 to 60 white cells per high-power field. All chemical features were within normal limits, except for slight elevation of alkaline phosphatase (4.4 B-L units) and a bromsulphalein retention was 5.9 percent. An x-ray film of the chest showed multiple densities bilaterally. A bone survey was negative. Determinations of 24-hour urinary chorionic gonadotropin were positive at 75,000 international units per 1,000 ml, negative at 90,000 units.

The patient continued to have vaginal bleeding which required transfusion replacement of blood and vaginal packing. Difficulty in voiding necessitated use of a Foley catheter. Because of the previously noted leukopenia, it was decided to start actinomycin D therapy. On 26 June 1 mg was given intravenously and then 0.5 mg a day for the next seven days. The patient also received vincristine, 0.5 mg on 28 June and 0.5 mg on 5 July.

DR. PREGER:* The chest film shows metastatic lesions. If we had obtained tomograms of both lungs, we would have seen additional lesions. An intravenous pyelogram does not show any abnormality of the kidney or evidence of any mass above the bladder. In summary, we have a patient with diffuse pulmonary metastatic lesions.

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*John J. Bagshaw, M.D., Resident in Medicine.

*Leslie Preger, M.D., Assistant Professor of Radiology.

Dr. Smith:* The patient is unable to be here for personal presentation this morning. We have asked Dr. Edwin M. Jacobs to open the discussion. As we know, this disorder has been the most promising malignant lesion with regard to therapy. We would like to ask Dr. Jacobs, who has had extensive personal experience, to tell us something about the natural history of choriocarcinoma and something about the result of chemotherapy. More specifically, we would ask: What would you do for this patient, and what would you anticipate?

Dr. Jacobs:† The problem presented by this patient is somewhat more complicated than the usual one of choriocarcinoma of the uterus, because she has had a number of complications. She has had vaginal bleeding which has persisted after hysterectomy and, for some unexplained reason, she has had leukopenia although her bone marrow appears to be within normal limits. Most patients with choriocarcinoma of the uterus are treated with an antifolic acid agent, Methotrexate®, in large daily doses. However, we felt that this would be unwise in this patient because of the continued bleeding and the compromised white count. At present we are using actinomycin D in conjunction with vincristine.

As Dr. Smith commented, this is one of the malignant diseases most exciting to treat. This condition allows the first encouraging results we have had in treating patients with widespread metastatic disease with chemotherapy. In fact this is the only cancer we can regularly cure by the use of a drug. The first report of such cures was published by Li in 1956.[8] Apparently this information is still not fully appreciated, so I think we should review briefly our general approach to the diagnosis and treatment of trophoblastic disease at the beginning of this discussion. The details of diagnostic procedures and our approach to therapy are outlined in a recent paper.[7]

First, one should suspect trophoblastic disease after an abnormal pregnancy, abortion, or delivery of a hydatidiform mole, if there is postpartum bleeding or persistence of a positive chorionic gonadotropin titer. One should suspect the disease when there is abnormal bleeding, chest pain, hemoptysis, dyspnea,[2] an unusually large and firm uterus, other masses in the abdomen, or neurological abnormalities (because of the possibility of brain metastasis). Dilatation and curettage should be performed promptly. The patient should also have a complete physical examination and a chest roentgenogram to determine if there is any evidence of metastasis. Of diagnostic value too is a 24-hour urine collection for determination of gonadotropin level. The determination should be performed by an accurate quantitative method in a qualified laboratory. An ordinary pregnancy test will not suffice. If the patient has choriocarcinoma, the chest film and intravenous pyelograms may show some abnormalities. The laboratory studies will show a high chorionic gonadotropin titer because the tumor contains trophoblastic tissue, and the cells are still active endocrinologically and secrete chorionic gonadotropin. They occasionally secrete other hormones, including a TSH-like substance, and in a few patients frank hyperthyroidism may develop as a consequence.[3] Thus, trophoblastic cells have an endocrine marker indicating their presence in the body.

If a diagnosis of choriocarcinoma is established or suspected on the basis of these studies, chemotherapy should be started immediately, for time is of the essence. The disease can progress rapidly. Dr. Hertz (National Cancer Institute), in a study of a large series of cases,[6] found that the patients with the best therapeutic responses were those who were treated within four months after appearance of their first symptoms. The patients who had a poor response or became resistant to chemotherapy were most likely to be those treated later than four months after diagnosis.

Even if the initial dilatation and curettage do not definitely indicate choriocarcinoma, the patient should be observed carefully during the ensuing month. If the findings are negative except for a positive gonadotropin titer, one should draw the conclusion that trophoblastic cells are present, and the patient should be treated, even though this titer might represent a more benign disease than choriocarcinoma. Hysterectomy should not be performed except to prevent bleeding. If the uterus can be spared, the patient's child-bearing potential is not sacrificed. If metastatic disease is going to be cured, the local disease will also be cured. Also, there is no good evidence that hysterectomy will aid in the cure of metastatic disease. According to Hertz, there is some evidence that those patients who have hysterectomy tend to have a poorer prognosis than those who do not.[6]

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*Lloyd H. Smith, Jr., M.D., Professor and Chairman, Department of Medicine.

†Edwin M. Jacobs, M.D., Assistant Clinical Professor of Medicine and Radiology; Assistant Research Physician, Cancer Research Institute.

We do not know why trophoblastic tissue of the placenta becomes malignant. A hydatidiform mole may develop, or one of the more malignant entities may develop. The etiology is unknown.

The incidence of hydatidiform moles in the United States is one in every 2,000 pregnancies, and about 5 percent of these become choriocarcinoma (that is 1:20,000-40,000 pregnancies). This is a relatively rare disease in the United States. By comparison, in the Philippines[1] the incidences of moles and of choriocarcinoma are considerably higher (moles, 1:200 pregnancies; choriocarcinoma, 1:2,000 pregnancies). This is thought to be due to childbearing at the extremes of the age range and to the high parity of most women in that country. Approximately 50 percent of choriocarcinomas occur after the passage of a hydatidiform mole, approximately 25 percent after an abortion, 22.5 percent after a normal pregnancy, and perhaps 2.5 percent after an ectopic pregnancy.

Trophoblastic disease has been recognized for many centuries. Tumors of the trophoblast were described by Marshand in 1895-1903. A pathologic classification was introduced by James Ewing in 1910. This was a somewhat complicated classification. There is a simplified one now: normal trophoblast, hydatidiform mole, chorioadenoma destruens (that is, malignant mole with local invasion or distant spread), and choriocarcinoma. There is no absolute pathologic distinction between these various types, which form a spectrum, and are now referred to as diseases of the trophoblast.

A considerable body of data obtained in recent decades gives us some interesting facts.[12] It has long been known that trophoblastic tissue does get into the blood vessels of pregnant women, and it has been thought that these emboli might play a role in eclampsia. There have been some early reports of deaths related to emboli. Experimental embolization in animals over many years showed no evidence of eclampsia. During the period 1949-1957 it was recognized that the trophoblastic tissue was a form of homotransplant. It has been referred to as an F_1 hybrid back-cross because half of the chromatin is from the female and half from the male. In other words, the trophoblastic tissue is a product of conception, and is a back-cross to the female. In certain strains of mice, tissue from female transplanted to female, or tissue from male transplanted to male, almost always "takes." But when tissue is transplanted from male to female, there are failures. It has been postulated that the presence of the Y chromosome results in the production of RNA of different base composition.

All of these factors might relate to the interesting fact that trophoblastic malignant lesions can be cured with chemotherapy and other malignant lesions can not.[9] It may be that a genetic difference plays a role. For example, Dr. Page* and coworkers have reported on the sex chromatin content of trophoblastic tumors.[11] They have shown that in hydatidiform moles almost 100 percent are of the XX type, whereas in choriocarcinoma they were mixed. One wonders if the response of patients with choriocarcinoma or their lack of response may in some way be related to whether the choriocarcinoma in a given instance is of the XX or XY type. This has not been fully worked out as yet.

In vitro cultures of trophoblast have been attempted, and human trophoblastic cells have been grown in the anterior chamber of the eye and in the cheek-pouch of cortisone-treated hamsters. All of these studies were attempted to demonstrate the presence of antibodies against trophoblastic tissue. It was thought that unusually good response in a patient might reflect antibody response against this form of transplant, but so far specific antibodies have not been discovered.

Spontaneous remissions have been reported in the range between 5 percent and 20 percent; these have been observed in patients with localized or relatively localized disease. In contrast, I do not know of a case of advanced metastatic choriocarcinoma in which spontaneous remission has occurred.

Early attempts at treatment were made by using antisera to trophoblast in these patients, and in one instance leukocytes from the husband were given to the wife. These results were equivocal at best. Finally in 1956, Dr. Li treated a patient for the first time with large doses of 4-amino-n[10] methyl pteroylglutamic acid (Methotrexate). Some of the background of this form of therapy is of interest. Hertz in 1948 showed that there was decreased development of the genital tracts in folic acid-deficient rats. Nelson and Evans (1951) later demonstrated a high fetal requirement of folate; and Thiersch (1953) found that abortion might result from the use of aminopterin, an anti-folic acid compound. In 1953 at the Memorial Center for Cancer and Allied Diseases, New York, Li studied a patient with malignant melanoma who had elevated chorionic gonadotropin titer. The reason for the elevated titer was not explained, but when this patient was treated with Methotrexate, it was noted that the titer dropped. Three years later, when Li (then at the National Cancer Institute) had a patient with widespread chorionic carcinoma, he recalled his earlier chance experience and decided to use Methotrexate in high dosage to treat this patient.

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*Ernest W. Page, M.D., Professor and Chairman, Department of Obstetrics and Gynecology.

A number of other chemotherapeutic compounds have been used. Karnofsky in 1950 treated a patient with nitrogen mustard (mechlorethamine hydrochloride) and obtained a transient remission of pulmonary metastatic lesions. But it was the introduction of Methotrexate in high daily doses by Li and Hertz[4,8,11] that first led to a significant number of cures. Actinomycin D, an anti-tumor antibiotic, has also been used. Two of the alkaloid extracts of the periwinkle plant, vincristine and vinblastine, have been used. Also 6-diazo-5-oxy-1-norleucine (DON) which is a glutamine antagonist, has been used successfully in treating some patients. In 1964, Dr. Hertz summarized the experience from the National Cancer Institute with various forms of treatment, mainly Methotrexate and actinomycin D, and reported a total response rate of about 64 percent.[5] In a more recent report over 70 percent of women with choriocarcinoma have been found to respond.[6] In our series of cases at the University of California San Francisco Medical Center,[7] we found that before chemotherapy was used no patients survived, even when disease was localized, with the single exception of a patient who had hysterectomy. Since then, with chemotherapy our cure rate has been 90 percent. One patient who entered the hospital in a terminal state with brain metastasis died within three days. In another patient cerebral hemorrhage developed after a complete radiological remission of disease. (See Table 1.)

I will present very briefly several representative cases. The first patient had metastasis to the abdomen, liver, lungs, and brain with many secondary complications. She was treated with 13 courses of Methotrexate over a period of 15 months but is alive and well today, now eight years later. An intravenous pyelogram in April of 1960 revealed hydronephrosis, massive on the right, moderate on the left. A post-therapy intravenous pyelogram showed a normal left kidney and residual hydronephrosis of the right kidney due to fibrosis. Serial x-ray films of the chest showed complete regression of numerous metastatic lesions.

Another patient, who was treated with ten courses of Methotrexate, had a relapse and subsequently was treated with actinomycin D. This patient required hysterectomy because of massive vaginal bleeding during therapy. Intravenous pyelograms during therapy indicated disappearance of abnormalities. The chest film of September 1963 showed massive pulmonary metastatic involvement. These lesions had disappeared by April 1965, and subsequent films have remained clear.

A third patient was treated with massive doses of Methotrexate with no response and was then treated with actinomycin D and chlorambucil, still with no response. She had massive pulmonary infiltrates, dyspnea and bone marrow depression. She was then treated with small doses of vincristine, once weekly. The disease has been in complete remission for the past three years. (See Chart 1 and Figure 1.)

Finally, I will describe one of Dr. Li's cases. The patient had metastatic choriocarcinoma and a high chorionic gonadotropin titer, and was

TABLE 1.—*Toxic Manifestations Associated with Chemotherapeutic Agents Used in Choriocarcinoma of the Uterus*

Agents	*Route of Administration*	*Usual Dose*	*Acute Toxic Signs*	*Major Toxic Manifestations*
4-amino-n^{10} methyl pteroylglutamic acid (Methotrexate®)	Intravenous	15 to 20 mg/day × 3 or 5	None	Oral and digestive tract ulcerations; bone marrow depression with leukopenia, thrombocytopenia, bleeding.
Dactinomycin (Actinomycin D)	Intravenous	0.01 mg/kg/day × 4 or 5 every 1-2 weeks or 0.04 mg/kg/ week	Nausea and vomiting	Stomatitis, gastrointestinal disturbances, alopecia, bone marrow depression.
Vinblastine (Velban®)	Intravenous	0.1 to 0.2 mg/kg weekly	Nausea and vomiting	Alopecia, areflexia, bone marrow depression.
Vincristine (Oncovin®)	Intravenous	0.01 to 0.025 mg/kg weekly	None	Areflexia, muscular weakness, peripheral neuritis, paralytic ileus, mild bone marrow depression.

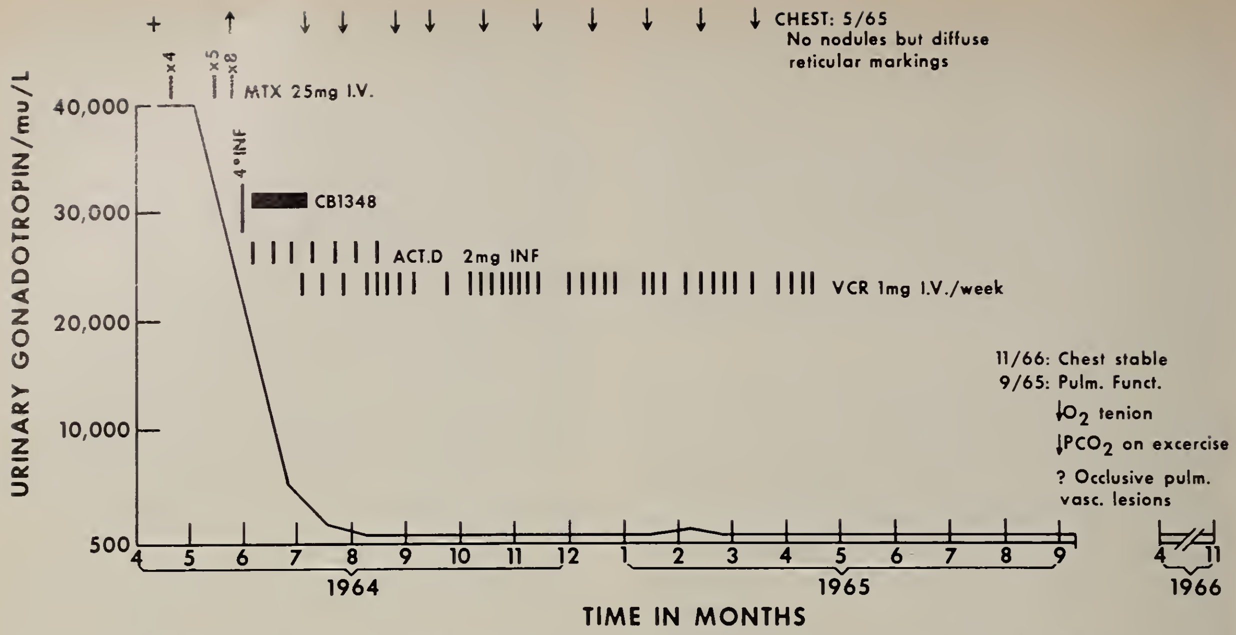

Chart 1.—Response to treatment of a patient with metastatic choriocarcinoma. No response to Methotrexate, actinomycin D, and chlorambucil. Complete remission with vincristine.

treated with Methotrexate. After apparent complete remission of disease and return of gonadotropin titer to zero, therapy was stopped. Subsequently the titer became elevated, and treatment was started again, but this time without alteration of the gonadotropin titer. The patient was found to be pregnant and, fortunately, gave birth to normal twins.

After a patient is apparently cured, contraceptive measures should be used during the following year. Since the gonadotropin titer is a major indicator of recurrence of disease or presence of trophoblastic cells, one may be treating pregnancy rather than recurrence unless alert to this possibility. It is simpler to follow the patient's progress if the possibility of pregnancy is eliminated. After a year of remission of disease, it is safe for her to become pregnant. Pregnancy appears not to increase danger of the occurrence of another choriocarcinoma. I know of no patient who has been cured for a year or more and then had relapse.

Dr. Smith: Thank you very much, Dr. Jacobs. You have brought out some very interesting facts concerning this group of malignant diseases, perhaps one of the most intriguing being that this represents the only malignant homotransplant. I don't think we have another example of a malignant homotransplant in a host, or one which has such an exquisitely sensitive biochemical marker in the form of chorionic gonadotropin to indicate whether malignant cells are present. Finally, there is the sensitivity to chemotherapy. You have answered one of my questions, which was whether choriocarcinoma was rather selectively sensitive.

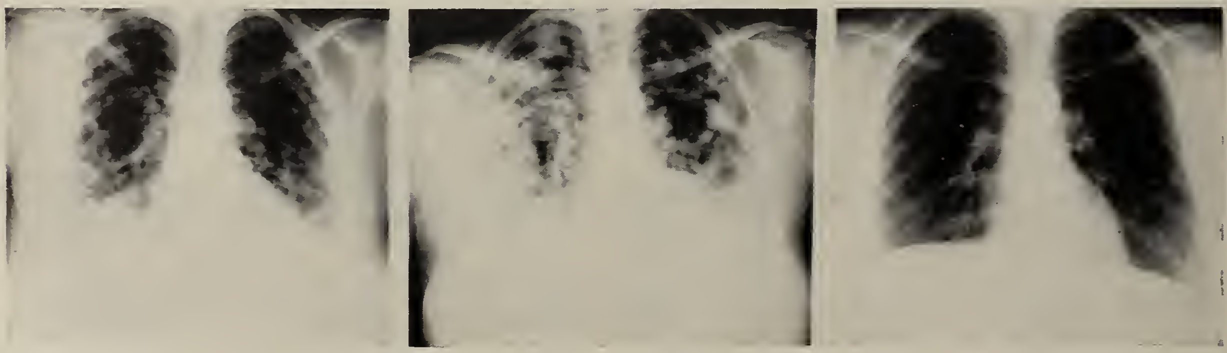

Figure 1.—Chest roentgenograms before therapy (left); showing disease progression after Methotrexate (center), and regression of metastases after vincristine (right).

Apparently, choriocarcinoma responds to a variety of chemotherapeutic agents.

QUESTION FROM THE AUDIENCE: Dr. Jacobs, who do you think should treat choriocarcinoma?

DR. JACOBS: This is a rare disease which physicians rarely see, and it is subject to the complications of aggressive chemotherapy, which were illustrated in our patient today. Because of these factors, I think that these patients are best treated by physicians who have had broad experience with this disease.

QUESTIONS FROM THE AUDIENCE: What is the response of male choriocarcinoma?

DR. JACOBS: The response of male choriocarcinoma is dismal. These tumors do secrete chorionic gonadotropins, and the titer is used as an indicator for therapy. However, these tumors are different genetically since they are autologous. They are very malignant tumors, and their response to chemotherapy is poor.

DR. SMITH: Thank you, Dr. Jacobs.

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SCHOOL PROBLEMS

"[In diagnosing the functional causes of school problems in children,] the most practical thing to do is to go where the trouble is. You cannot sit in your office and find out one tenth of what you can find out in a school in one-fifth the time. I've discovered, particularly in fairly stable schools where the faculty has worked for a good while and where they don't have the 50 or 60 percent turnover characteristic or large urban schools, that you can sit down for about 45 minutes with a collection of teachers, principals, the nurse, perhaps the school physician if you can catch him, and the school social worker and say, 'Tell me why you are concerned, and then let's hear all you know about the family, the brothers and sisters and the parents.' You will find that many of these teachers have taught the parents and also are acquainted with the grandparents. So that quite often in a few minutes you can gather a very rich, detailed, three-generational social, medical, and educational history of a child which would take you weeks and weeks of our usual, laborious clinical interviewing methods to gather."

—STONEWALL B. STICKNEY, M.D., Pittsburgh
Extracted from *Audio-Digest Pediatrics,* Vol. 14, No. 20, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

Alcoholism

Its Present Legal and Medical Status

ALFRED AUERBACK, M.D., *San Francisco*

ALCOHOLISM IS A MAJOR health threat exceeded only by heart disease, cancer and mental illness. There are more than five million alcoholics in the United States and an estimated 200,000 new cases each year. More than a million of the alcoholics have physical or psychological illnesses as complications of their alcoholism. Physical disorders include cardiac, pancreatic or liver damage, gastritis and other gastrointestinal diseases, polyneuritis and degenerative changes in the central nervous system. Psychological disorders include personality changes, delirium tremens or psychotic states. Excessive drinking is a slow, insidious, malignant disease—a major cause of death in the age group of 35 to 65. The life expectancy of alcoholics is 10 to 12 years less than that of the nonalcoholic. Among the common causes of death are liver or heart failure, gastrointestinal hemorrhage, accident, suicide or acute intoxication. The physical debilitation and poor nutrition of these persons render them susceptible to all forms of intercurrent illness.[1]

Medical Attitudes Toward Alcoholism

Until recently alcoholism was considered a moral problem. The alcoholic was thought to be a bad or weak person who lacked the will power to stop drinking. In 1956 the American Medical Association adopted a resolution stating that alcoholism, "which occurs in many personality disorders, comes within the scope of medical practice," that "acute alcoholic intoxication can be and often is a medical emergency" and that "in order to offer house officers well-rounded training in a general hospital there should be adequate facilities available as part of a hospital program for the care of alcoholics." The resolution said further: "Since the house officer in a hospital eventually comes in contact with this type of patient in practice, his training in treating this illness should come while he is a resident officer. Hospital staffs should be encouraged to accept these patients for treatment and to cooperate in this program."[2]

The American Medical Association has restated this position regarding alcoholism on repeated occasions in recent years. The American Hospital Association has recommended that general hospitals accept alcoholics for treatment under this diagnosis. However, a recent survey indicated that two-thirds of the general hospitals in the United States do not admit patients for alcoholism. Only 35 of the nation's 250 state mental hospitals have special treatment programs for alcoholics.[3]

Most physicians in private practice encounter patients with drinking problems. In July 1964 a survey[1] of 695 physicians in San Francisco indicated that 76 percent handled patients with a drinking problem. Half of them provided only medical care and made no effort to counsel or refer the patient to specific treatment agencies. The remaining physicians provided medication and counselling or directed their patients to a hospital, clinic, psychiatrist, clergyman or Alcoholics Anonymous, as the case warranted. Physicians generally have found patients who drink excessively to be difficult, demanding and often uncooperative. Only a small number found them interesting or worthwhile patients. This tendency to reject the alcoholic led to an editorial in the Journal of the Michigan State Medical Society criticizing physicians who would not treat alcoholics as failing to meet their medical obligations.[4]

Submitted 28 January 1969.
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Legal Attitudes Toward Alcoholism

The legal profession has long been disturbed by the problems of the alcoholic. Law enforcement officials estimate that 40 percent of all arrests in the United States are for drunkenness. Intoxication is a factor in half of all driving fatalities. The tendency has been to arrest the alcoholic for public intoxication or vagrancy, with one to three months in jail as a consequence.

However, in the last few years there has been a radical change in the legal handling of the alcoholic. Federal appellate courts in Virginia and the District of Columbia in 1966 overturned the conviction of two men sentenced to jail for public intoxication. In 1967 a Georgia state court ruled that alcoholism is an illness, not a crime for which a person can be jailed. As a result it ruled that all persons apprehended by the police for drinking must be examined by a physician to determine the diagnosis.

The effect of these legal rulings on the handling of alcoholics in cities such as Washington or Atlanta showed that the medical profession was not prepared to cope with the problems of alcoholism. After the decision in the District of Columbia in 1966 the court there began committing suspected alcoholics to the district public health department for diagnosis and treatment. But the department had only about 50 hospital beds and an out-patient clinic available for treating alcoholics, and chaos developed as its facilities were overwhelmed with patients sent by the court. In less than a year more than 4,000 persons in the District of Columbia had been declared alcoholics and, as such, immune to jail sentences for drunkenness.

In Atlanta where drunkenness is the reason for 55 percent of all arrests, the hospitals and clinics were flooded with court-referred alcoholics. The Georgian Clinic in Atlanta, a state facility for the treatment of alcoholics, quickly had a six month waiting list with no money for any increase in treatment programs. In St. Louis the police were taking drunks directly to a detoxication center instead of to jail. Here, as everywhere else, the medical facilities to cope with the court referrals proved hopelessly inadequate.

Across the United States hospitals and medical groups became alarmed at this trend in handling alcoholism. With the courts now accepting the statements of organized medicine that alcoholism is an illness, persons with drinking problems were being referred to medical facilities for diagnosis and treatment instead of being jailed. Nowhere were out-patient or in-patient facilities or trained staff available to cope with the flood of referrals.

During early 1968 the situation appeared even more grim in light of a case being considered by the U.S. Supreme Court. In Texas a man named Leroy Powell had been convicted of public intoxication after a physician had testified, in his defense, that he was a chronic alcoholic. He appealed the conviction to the Supreme Court with legal help from nine organizations, including the American Medical Association, the American Civil Liberties Union and some church groups. It was expected that the Supreme Court would continue the trend of the lower courts in ruling that alcoholism is an illness for which a person should not be imprisoned. However, in June 1968, the U.S. Supreme Court ruled that the jailing of chronic alcoholics for public drunkenness does not violate their constitutional rights. Excerpts from the court opinion are of critical importance to the medical and legal professions. The decision, while apparently reversing a humanitarian trend, actually pointed out the direction in which medicine must go to cope with this increasingly serious medical and social problem.

The Supreme Court Decision

Excerpts from the court decision written by Justice Thurgood Marshall follow[5]: "Facilities for the attempted treatment of indigent alcoholics are woefully lacking throughout the country. It would be tragic to return large numbers of helpless, sometimes dangerous and frequently unsanitary, inebriates to the streets of our cities without even the opportunity to sober up adequately which a brief jail term provides. Presumably no state or city will tolerate such a state of affairs. Yet the medical profession cannot, and does not, tell us with any assurance that, even if the building, equipment and trained personnel are made available, it could provide anything more than slightly higher-class jails for our indigent, habitual, inebriates.

"Thus we run the grave risk that nothing will be accomplished beyond the hanging of a new sign, reading 'hospital,' over one wing of the jailhouse.

"One virtue of the criminal process is, at least, that the duration of penal incarceration typically has some outside limit; this isn't universally true in the case of petty offenses, such as public drunkenness, where jail terms are quite short on the whole.

"Therapeutic civil commitment lacks this feature. One is typically committed until one is cured. Thus to do otherwise than affirm [the appellant's conviction] might subject indigent alcoholics to the risk that they may be locked up for an indefinite period of time under the same conditions as before, with no more hope than before of receiving effective help and no prospect of prompt release.

"Faced with this unpleasant reality, we are unable to assert that the use of the criminal process as a means of dealing with the public aspects of problem drinking can never be defended as rational. The picture of the penniless drunk propelled aimlessly and endlessly through the law's 'revolving door' of arrest, incarceration, release and re-arrest is not a pretty one.

"If, in addition to the absence of a coherent approach to the problem of treatment, we consider the almost complete absence of facilities and manpower for the implementation of a rehabilitation program, it is difficult to say in the present context that the criminal process is utterly lacking in social value.

"We are unable to conclude, on the state of this record or on the current state of medical knowledge, that chronic alcoholics in general, and Leroy Powell in particular, suffer from such an irresistible compulsion to drink and to get drunk in public that they are utterly unable to control their performance of either or both of these acts and thus cannot be deterred at all from public intoxication.

"It is simply not yet the time to write into the Constitution formulas cast in terms whose meanings, let alone relevance, are not yet clear either to doctors or lawyers."

Discussion

The Supreme Court decision indicates that the law is looking to the medical profession to consider alcoholism and the problems of excessive drinking in the light of its statement that alcoholism is an illness. Up to the present, physicians have shied away from accepting their responsibility in connection with this serious disorder. In addition to the physical ailments due to excessive drinking, we must face the other costs. It has been estimated that *every* alcoholic adversely affects the lives of at least four other persons—wife, children, employer, friends and relatives. At least 25 million persons are hurt by the immoderate use of alcohol in this country. The emotional and financial loss caused by marital strife, broken homes, neglected children, impaired work performance, lost employment, hospitalization, accidents, deaths, injuries and arrests represent a staggering total.

The medical profession must face its responsibilities in coping with a disorder that affects so many people in so many ways. There must be more treatment facilities involving a multi-disciplinary approach using medical, phychological, sociological, legal and religious aids and involving all those individuals and the groups in the community who have an interest or concern. Business and industry must recognize that 5 percent of their work forces have a drinking problem. Experience has shown that many alcoholics can and do recover when given appropriate treatment.

The courts of this country have shown their willingness to reassess the legal handling of the alcoholic when the medical profession assumes its rightful role in combatting this grave disorder.

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In the Forefront

The Hunters Point-Bayview Community Health Service

(A Project of the John Hale Medical Society, the San Francisco Chapter of the National Medical Association)

ARTHUR H. COLEMAN, M.D., J.D., *San Francisco*

IN THE EARLY part of 1967 a group of neighborhood people spearheaded by the author felt that a new and innovative approach was needed to improve the delivery of health care in a community in which, for one reason or another, health care was not widely enough available or well enough used. The community involved, known as the Hunters Point-Bayview district of San Francisco, contains several hard-core areas of low income and other disadvantages, such as are typically found in most metropolitan areas today.

The area to be served by the effort to improve health care covers five census tracts and contains approximately 55,000 people. Of this number, approximately three-fifths are white. The sections in greatest need in the area comprise public housing occupied by about 15,000 persons, 90 percent of whom are black.

In trying to create a new approach, the group was aware of the writings of Professor Anselm Strauss of the University of California Medical Center. In a paper written for the Institute for Policy Studies, Washington, D.C., entitled "Medical Organization, Medical Care and Low-Income Groups," Dr. Strauss questioned whether low-income Americans would realistically expect anything like equality of care without considerably more far-reaching reforms in our present system of medical and health care delivery than are instituted by present legislation or assumed in current planning. His argument was that it is erroneous to assume that the system of medical organization is basically sound, and that medically disadvantaged groups can be reached without radical transformation of this system. He further said that, with that error at its base, the further assumption that more financial support, manpower, and various other kinds of resources are needed must also fail. These resources, he noted, "are used principally for improved efficiency of the present system but do not alter or modify the delivery of services to these groups." Moreover, Dr. Strauss said, "the placing of centers in the low-income locale [is not] the solution, since a study has shown that this does not in itself draw sufficiently upon the population to make 'much of a dent' on low-income illnesses."

After several community meetings, the consensus of the group was that delivery of health care to the poor would never be effectively improved unless changes could be brought about in the life style of the poor, particularly with regard to their attitude and behavior toward health care. As most physicians know, the poor generally delay seeking health care until it becomes an emergency. In other words, they are crises-oriented. Such delay may be due in part to ignorance or poor health habits, but frequently it is due to social, cultural and economic obstacles beyond their control. A missed appointment may not be the result of indifference, but quite often due to lack of transportation, to baby-sitting problems, or even to lack of car-fare money to and from the physician.

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The community group also felt that a double standard of health care should be eliminated. The clinic approach, regardless of how it may be "dressed up" in the new programs which are being set up throughout the country, has never met the real needs of the poor, especially the black poor. As an illustration, deaths per 1,000 from cancer of the cervix in white women from 1940 to 1963 dropped from 22 to 16. In black women during this period, it did not significantly change—30 to 29. The feeling of the community group was that Title XIX of Public Law 89-97 (the amended Social Security Act of 1935) should be strongly implemented by allowing the poor to have freedom of choice and directing them, as much as is feasible, into the private sector of health care. Just as a dual system of education is inherently unequal and morally wrong, so is a double standard of health care. The group concluded that four steps were mandatory; we must

1. Provide freedom of choice of physicians or health facilities, as much as is feasible.
2. Make maximum use of existing facilities, preferably private when feasible.
3. Affect the life style of the poor as it relates to health.
4. Bring some impact upon the providers of health services to change their attitude toward the poor.

The method to achieve the foregoing entails establishing four health teams. Each team will consist of a public health nurse, a social worker, a secretary and six social health technicians. The latter are community non-professional people who are to be given a 26- to 30-week training period while on the job. They are called social health technicians because they will deal with the social problems of the family or individuals with the ultimate goal of improving the family's or the individual's health.

The teams will spend 80 to 90 percent of their time in the field. Contact with cases will be made by "cold canvass" (knocking on doors) and by referrals from other agencies, neighbors or the client-patient. Great emphasis will be placed on follow-up. It is not enough to tell the poor where to go for help for they frequently get lost in or become frustrated by bureaucracy. Hence, where indicated, they will be accompanied to the hospital, to a physician's office or to whatever agency can be useful in a given situation.

In specific cases where follow-up appointments are in order and the patient has been known to be a chronic "appointment misser," a team member will try to develop the rapport and intimacy of contact so that he or she can call on the patient to encourage or persuade him to keep his appointments for his own good. However, we will constantly keep in mind that we are not to make people dependent upon us. The focus, thus, in helping will be to develop self-help by the client-patient. Our goal will be to assist him only to give him the confidence he needs to build self-reliance.

A research-evaluation component has been built into the program. The research department is headed by a social scientist. At present, several studies are in the active stages.

1. To determine the community's attitudes toward health.
2. To determine the power structure in the community. Once the key people have been identified, then we can establish a relationship with them to assist us in developing new policies for the program.
3. To determine the lines of communication in the community. Once known, then it becomes simple for us to tap in and feed information about the program to the community as well as receive information.
4. Multiphasic screening through the San Francisco Kaiser Hospital will be done on 200 heads-of-household and 50 children in the area (chosen through a random sample process) to establish a baseline of what the disease process of the community is at this time. Funds are not available for a larger sample, but the project will be open-ended.
5. As an extension of the first four stages, we are seeking funds so that the information obtained from the studies can be distributed for consumption by the community in language or through media understood by them. One of the reasons low-income groups resent research on them is that they never hear about the results and never see any direct benefits—their life situation does not change. To put it bluntly, they feel exploited, and understandably so. The researcher, for his study of the ghettoes, gains recognition and honors from his peers; the researched person in the ghettoes remains jobless, homeless and in despair.

By giving the community the results of our studies, we hope to provide it with a concrete tool of specifics to help in plotting a course toward improving the health of the community.

In November 1967 the John Hale Medical Society, the San Francisco Chapter of the National Medical Association, submitted to the United States Public Health Service a proposal for a five-year project to be funded under Public Law 89-749 (Comprehensive Health Planning). A grant of $705,046 was awarded for the first year's budget starting 1 July 1968. Six months from the funding date, the program had been administratively organized, all of the staff had been hired with the exception of two of the teams (which will have been staffed by the time this appears), office space has been secured and utilized (there has been no need to build an elaborate clinic facility since direct medical services are not given), and over 100 cases have been assisted. This type of project points out the speed with which the program can get started and time is of the essence these days.

I would repeat that the mere establishment of a physical plant will not greatly alter the behavior of large masses of poor people—a shining example of this is public housing. We must give direct attention to the low-income consumer and affect his life style directly in our future planning for improving health care delivery to this group. Freedom of choice should be maintained at any cost.

DIAGNOSTIC PEARLS FOR THREE NEW PEDIATRIC SYNDROMES

"One should be aware of the syndrome of Bassen-Kornzweig (or a beta lipoproteinemia) in an infant or child who has . . . large foul-smelling stools, who fails to thrive, whose sweat chloride levels are normal, and who does not have recurrent pulmonary infections. The pearl I would suggest is to look at the peripheral blood smear and look for the very peculiar-looking red cells which are rather pathognomonic of this entity. This is a malabsorption syndrome, far less common than cystic fibrosis and celiac syndrome, but does occur and has been reported much more frequently in the last few years.

"One might think of the Toulouse-Lautrec syndrome (pyknodysostosis) when one sees a child who has frequent fractures, whose x-rays show increased brittleness or density of the bones, whose cranial sutures fail to close, whose hands are deformed, and whose chin recedes. All children who are short and squat are not achondroplastic; some may well have this syndrome of Henri de la Toulouse-Lautrec.

"The third syndrome, fatal granulomatous disease of childhood, can be picked up; but this requires certain complicated laboratory tests to determine the phagocytic activity of the neutrophils. There are no real pearls for the practioner in his office without the help of a good hematologic laboratory. However, most of the patients are males, and most of them have chronic suppurative lymphadenitis; and I think knowing this should alert one to the possibility of this particular syndrome."

—Thomas E. Cone, Jr., M.D., Boston
Extracted from *Audio-Digest Pediatrics,* Vol. 14, No. 21, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

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EDITORIAL

Guest Editorial

Choriocarcinoma and Related Trophoblastic Tumors in Women

OUR OBSERVATIONS OVER the past 12 years have led to the concept that the gestational trophoblastic disease constitutes a continuous biological spectrum which may present itself morphologically as hydatidiform mole, invasive mole (chorioadenoma destruens) or choriocarcinoma. The histological criteria for delineating these entities are sufficiently specific to permit morphological classification when adequate tissue is carefully studied.[1,2,3] However, numerous cases are readily misdiagnosed even by expert observers. Our data show that such purely morphological considerations have little bearing on the final response to appropriately applied chemotherapy.[4,5,6,7]

The most definitive criterion for the evaluation of chemotherapy is the behavior of the urinary chorionic gonadotropin titre. Accordingly, great emphasis is placed on the careful collection and refrigeration of complete 24-hour urine specimens and upon meticulous care in the concentration and bioassay of these specimens. To date, we have found no bioassay system superior to the mouse-uterine-weight method for the detection of minimal traces of residual disease. Other bioassay or immunoassay systems such as those currently used for the diagnosis of pregnancy are not sufficiently sensitive for this purpose. Some laboratories have found that exquisitely sensitive radio-immunoassay methods applied to serum are suitable for monitoring chemotherapy. Not enough time has elapsed to permit definitive correlation between such radio-immunoassay results and the clinical course of disease through several years of follow-up. Nevertheless, it appears highly probable that radio-immunoassay may soon be able to replace bioassay for such critical determinations.

The duration of the disease process and the associated extent of disease before therapy are decisive factors in determining the results of chemotherapy. In patients with metastatic disease whose course is less than four months in duration before chemotherapy is begun and whose initial urinary titre is less than 100,000 I.U. per 24 hours, we may expect a 95 percent complete remission rate.[5,7] In patients with a longer history and with higher initial titres the complete remission rate falls to 36 percent. The necessity for early diagnosis and prompt treatment can not be overemphasized.

An extension of this principle is also demonstrated by the almost uniform eradication of early non-metastatic trophoblastic disease by primary chemotherapy in place of hysterectomy, thus preserving reproductive function for these women.[6,8]

The severe toxicity imposed by intensive, intermittent regimens of Methotrexate or actomyocin

D will prove entirely reversible in patients whose renal, hepatic and hemopoietic functions are shown to be normal before therapy, provided such patients are given the benefit of adequate laboratory and clinical surveillance during and after treatment.[5,7,9,10]

The endocrinological study of patients with trophoblastic disease indicates that some tumors produce a thyreotropic substance, thus inducing a hyperthyroid state in the host which responds to specific onclytic therapy.[11,12]

Patients with trophoblastic disease differ endocrinologically from normally pregnant women in failing to exhibit increasing levels of urinary estrogen excretion. They also exhibit much lower levels of serum placental lactogen in proportion to the gonadotropin titre than one observes in normal pregnancy.[13] These biochemical differences may not only provide a practical basis for differential diagnosis but also lead to further comprehension of the nature of the metabolic derangements occuring in neoplastic trophoblast. Such analyses will be greatly facilitated by the ready availability for basic study of human choriocarcinoma maintained as heterologous transplants in the untreated hamster's cheek-pouch. More recently such tissue has been maintained in the brain of untreated monkeys as well as in tissue culture.[14,15,16]

The practical as well as the fundamental advances in the area of trophoblastic tumors during the past decade has been both gratifying and exhilarating. Nevertheless, there remain major challenges for further study especially with respect to etiology, pathogenesis, epidemiology and treatment.

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A Sequence of Change

IT IS INCUMBENT upon us to continue to examine the profound changes which are occurring in attitudes toward health and well-being, and as a profession we must do our best to prepare ourselves for what is likely to be a new order of things. There seems to be a certain sequence which is worth noting in many of these changes. Passive acceptance, or even indifference, gives way to a more positive emphasis on equality, conformity and acceptable standards, which in turn gives way to a more activist, at times militant, emphasis on individual fulfillment and self-realization, even to the point of non-conformity. This sequence may be seen in attitudes of people toward themselves, toward others, toward health and toward health care.

People are viewing themselves and their lot in life with changing attitudes. Gradually yesteryear's more or less passive acceptance of one's place in the social or economic scale was almost wholly displaced by the idea that one man is as good as another, and now this notion of equality among men is already being eroded by an increasing emphasis on individuality and the right to personal expression and fulfillment. In their attitudes toward others who are less fortunate, people are replacing indifference, neglect or even repression with individual and group voluntary efforts, and even massive governmental programs to help bring about conformity with going standards, on the assumption that this will be good for those who are being helped. This approach, in turn, is being somewhat disintegrated by the demand of the less fortunate that they simply be given the right and the wherewithal to try to solve their own problems as a matter of self-determination and self-expression.

A parallel sequence of change is occurring in attitudes toward health. The relatively passive acceptance of the ailments to which the flesh is heir, so characteristic of a generation ago, is now being replaced by a massive determination to bring health and health care equally to all people—the definition of health and health care in this context being supplied by those who know or think they know what good health ought to be. But again, clearly in the offing and rapidly approaching, is a more personal and self-fulfilling concept of health as a state of individual physical, mental and social well-being and not merely the absence of disease or infirmity.

Attitudes toward health care are following the same sequence. Formerly considered a privilege (which was granted to the unprivileged by compassionate physicians and compassionate institutions), health care has now become a right to which all are entitled. But the entitlement still pertains only to equal access to services for the prevention and treatment of injury, illness or infirmity. Health care has yet to adapt to the new focus on health as a state of well-being and self-fulfillment which is soon to come. When this occurs, neither health nor health care can any longer be considered as they so often are today, simply as products or commodities to be distributed by one or another kind of delivery system.

Thus there is certain to be a new order of things. The new order will likely be more familiar territory for physicians, many of whom have never been impressed by the success of statistically based stereotypes of health care which, some suspect, often give more satisfaction to the statisticians or health care planners than to the recipient who is supposed to benefit. The new focus will in fact be a renewal of the traditional emphasis of medicine which seeks to overcome any weakness or impairment in the patient, help him develop his capabilities and, upon occasion, to modify his life situation so that he may achieve health or its closest possible approximation in the circumstances. This new concept of health as a state of complete physical, mental and social well-being should fit like an old glove.

Gout and Hyperuricemia

In a sense we all have inappropriate hyperuricemia. Two errors in evolution have led us into this state of purine peril. First, the sensible enzyme uricase, which catalyzes the conversion of relatively insoluble urate to soluble allantoin, was somehow jettisoned. The resulting requirement for the excretion of uric acid would seem to have no biological advantage for the mammalian kidney. On the contrary, it constitutes a source of hazard. It is true that uricotelic metabolism is useful for bird and reptile in that uric acid can be excreted as an inspissated paste with resulting water conservation. It is a good cloacal chemical, as we are reminded from the defacement of public statuary, but poorly adapted for soluble transport and excretion. With uricase there would be no gout. A second error compounds the first. The mechanism by which the human kidney excretes uric acid is complex, representing glomerular filtration, tubular reabsorption, and tubular secretion. The net result is renal retention of greater than 90 percent of that filtered. At equilibrium the same amount of uric acid is excreted but at the cost of relative hyperuricemia. Other primates, and a single healthy man discovered by chance,[1] do not have renal reabsorption of filtered uric acid and therefore have serum uric acid levels of less than 0.5 mg per 100 ml. Gout therefore is a legacy of evolution, which may err as well as triumph.

Elsewhere in this issue of California Medicine Dr. James Klinenberg has presented an admirable review of many of the current concepts of purine metabolism and gout.[2] Gout is an antique disease from the clear evidence in a mummified Nubian toe and from the clinical observations of Hippocrates, cogently stated in three of his aphorisms. Its fortunes have undulated over the centuries. Sydenham, sometimes called the Shakespeare of gout, suffered long from the disease and wrote eloquently about it. Some of his words ring strangely from the pen of one himself inflicted: "The gout generally attacks those aged persons who have spent most of their lives in ease, voluptuousness, high living, and too free use of wine and other spiritous liquors." With this kind of authority it is perhaps not surprising that gout came to occupy a unique position as a disease in caricature in the seventeenth, eighteenth, and nineteenth centuries. Many of these cartoons and prints have been published in an amusing review entitled "A Gallery of Gout."[3] Gout, which never ceases to amaze its students, has slowly been resurrected in recent years from the butt of satire to the solace of intellectual and social preeminence. "The disease of kings, king of diseases" has allegedly afflicted an array of men of genius—Newton, Harvey, Milton, Johnson, Fox, Pitt, Franklin, Tennyson. Several recent studies have confirmed a positive statistical relationship between serum uric acid concentration and intelligence or social status.[4,5] In this context it is possibly unkind to recall that gout is rare in the premenopausal female.

In the past two decades many of the tools of modern biological investigation have been utilized with great success in clarifying the pathway of purine biosynthesis and the mechanisms by which its appropriate rate control is normally achieved. In subsequent clinical investigations this body of information has been applied to the study of patients with gout, first *in vivo* and more recently in enzymatic studies of hemic cells or tissue cultures of "gouty" fibroblasts. From this work it has become clear that there are a number of forms of gout pathogenetically, having in common the production of sustained hyperuricemia. At least five forms of gout occur: primary (genetic) overproduction gout of two types (the Lesch-Nyhan syndrome of hypoxanthine-guanine phosphoribosyltransferase deficiency and overproduction on some other as yet undefined genetic basis), secondary overproduction gout (myeloid metaplasia, polycythemia vera, and other proliferative disorders), primary (genetic) renal gout representing underexcretion, and secondary renal gout (renal disease or the uricoretentive effect of certain drugs or metabolites, such as lactic acid or β-hydroxybutyric acid). It can be safely predicted that further heterogeneity of the genetic forms of gout will be demonstrable in the early future as specific enzymatic defects. This may allow clarification of the modes of inheritance which, with the exception of the Lesch-Nyhan syndrome, are now in dispute. More importantly, it may also allow for more rational forms of therapy.

One of the achievements of the past few years has been the demonstration that acute gouty arthritis represents microcrystalline synovitis. This acute inflammatory response can be induced by the intra-articular injection of a number of crystals susceptible to phagocytosis and perhaps capable of activation of Hageman factor. Central to the response is the presence and presumably the metabolic activity of the leukocyte, although the relative contributions of kinin formation, the release of lysosomal enzymes, and other biochemical concomitants of phagocytosis have not been established. If the interaction of leukocyte and microcrystal is the basic event, it may prove feasible to use this simple model in the development of more effective and specific anti-inflammatory agents for acute gout. It is interesting to consider that gout as microcrystalline synovitis was first demonstrated quite convincingly by Freudweiler in His's laboratory at the beginning of the century.[6] This contribution was lost in the sediment of subsequent work, only to be unearthed after the phenomenon itself was quite recently rediscovered. Was Mr. Hageman susceptible to microcrystalline synovitis? Could patients with certain leukocyte dysfunctions, such as chronic granulomatous disease, exhibit reaction of this type to intra-articular crystals? Much remains to be learned about acute gout.

By and large the treatment of gout is now quite satisfactory in the majority of patients. If hyperuricemia can be controlled, sodium urate should not precipitate as microcrystals in or around joints to cause inflammation or as tophi in susceptible tissue. At least this is dogma, although the recent demonstration of protein binding of plasma urate complicates this simple interpretation.[7] In addition all physicians who treat gout are plagued by recurrence or exacerbation of acute arthritis during the early phases of therapy despite control of hyperuricemia. In theory reduction in the concentration of a metabolite can be obtained by three methods: (a) increase its rate of catabolism, (b) increase its rate of excretion, (c) reduce its rate of synthesis. One quarter to one-third of uric acid synthesized is normally catabolized by bacterial action following its excretion into the gut. No method has as yet been discovered to increase the destruction of uric acid by enhancing its excretion into the gut (other than to raise plasma uric acid levels). The uricosuric agents now available, on the other hand, are relatively specific, potent, and usually well tolerated. Most would agree that the use of such a drug still represents the first line of defense in the usual patient with gout in the absence of renal disease, uric acid nephrolithiasis, or massive tophaceous deposits. The most logical treatment would be to diminish urate synthesis. The discovery of allopurinol as an effective competitive inhibitor of xanthine oxidase has therefore marked a major therapeutic advance, the implications of which are still being evaluated. By use of this agent one genetic disease, gout, is converted pharmacologically into the biochemical equivalent of another genetic disease, xanthinuria. The patient benefits from this reshuffling of his purine end-products into more soluble forms. Perhaps the future will bring more precise control of *de novo* purine biosynthesis by pseudo feedback control.

In 1683 Sydenham wrote: "As for a radical cure, one altogether perfect, and one whereby a patient might be freed from even the disposition to the disease [gout] — this lies, like truth, at the bottom of a well; and so deep is it in the innermost recesses of Nature, that I know not when or by whom it will be brought forward into the light of day." The well is still deep and will contain still further surprises for those who dip into it.

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Indigenous Health Aides

For years it was almost an article of faith among many that the poor and a number of ethnic groups were not receiving the health care they needed primarily because of financial barriers. But evidence is now accumulating that while financial barriers are important, they may be quite subordinate to other even more fundamental constraints. In theory at least, Title XIX of the Medicare Law as it has been implemented in California's Medi-Cal program should completely remove the financial barrier for these needy segments of the population and should permit them freely to enter the mainstream of health care. Yet this has not occurred to the extent which might have been anticipated. Some of the reasons are now becoming evident.

First of all, there appears to be a sharp difference in motivation toward health care between those who by tradition or training give health a high priority in values and those who do not. It has too often been assumed by those who do, that everyone else does likewise. At times this has resulted in frustrations for those who have sought to do good for their less fortunate fellow men. It is also often overlooked that health and health care must be valued quite highly by someone before he is willing to experience or to even risk experiencing something which might be unpleasant, just because it might be good for his health. For example, many and various efforts to reduce smoking or the consumption of an excess of alcohol have only succeeded slowly if at all. In many cultures and social settings there is a reluctance to take an injection which may be painful or cause a reaction in order to prevent a disease which one may not get anyway. And in all walks of life there are persons who postpone or neglect going to see a physician, even when there are worrisome symptoms, for fear there may be something wrong which will bring even further unpleasantness into their lives. Thus, while there is general agreement that it is a good thing to be healthy, there remain many, especially among the poor and certain ethnic groups, who must become informed, convinced, motivated and shown how to utilize the health care services which they need if they are to take advantage of what modern science can do to improve one's health.

This is a serious problem. Experience has demonstrated that professional medical personnel are too often unable to communicate health information or to motivate those segments of the population which may be less educated, or disinterested or occasionally even hostile. The customary techniques of health education have somehow missed the mark. But evidence is growing that indigenous Health Aides, persons who are drawn from within the population to be reached and given a minimum amount of training, can become an effective means of breaching this kind of communications barrier. With relatively little formal training they are capable of motivating persons within a particular ethnic or poverty group to understand and seek the health care they should have. They can also identify and help to overcome the administrative and logistical difficulties which are so often present.

Two articles in this issue of CALIFORNIA MEDICINE (pages 207 and 253) deal with the use of indigenous Health Aides to assist in bringing the poor and certain ethnic minorities into the mainstream of modern health care. This approach appears to be both logical and successful. If so, it should be continued and extended. Mainstream health care for all is the goal which must be achieved. Anything less is not good enough for Americans in the latter half of the twentieth century.

The Fear of Women— Or Our Debt to Book Reviewers

ALTHOUGH THE SERVICE they perform is a valuable one that usually calls for a scholarly rounding of considerable degree, book reviewers are not often celebrated as they deserve for the work they do. Occasionally, however, one must deal with the accumulating debt we owe them, and it is pleasant to have our attention drawn to the general subject of book reviews by an outstanding example. In less than a page of type the reviewer of *The Fear of Women* (page 280) contributes a graceful essay that informs, provokes, entertains. We are told something of the book, something of its author, and, by inference, something of the essayist himself. (He comes through as a person of amiable disposition who has read widely and at some time has, say, worked on a road crew or a drilling rig or shot a little pool.) His review gets neatly down to the sum of the matter — the answer to that question the reader starts with and ends with: Shall I buy the book?

Our purpose here is not merely to call attention to the particular felicity of this review but to acknowledge the inadequately rewarded toil of our book reviewers in general. How very much they lighten the load of all of us who must read selectively or fall behind! Of them we can say, as the reviewer of *The Fear of Women* says of the author of that work: "We need guys like this around today."

ANGIOGRAPHY IN BLUNT ABDOMINAL TRAUMA

"Blunt abdominal trauma poses problems in both the diagnosis and the management of the various organs that are involved. The angiogram can solve many of these problems. In terms of problems in diagnosis, the patient with multiple injuries, the patient who is unconscious or intoxicated, the patient who might have a ruptured spleen is, of course, commonly recognized; but with regard to treatment, we're still not certain which renal injury—when identified—requires early operation, or what to do with the pelvic fracture in which there is massive bleeding, or exactly how to treat injuries to the liver. We have performed over 100 aortograms in patients with blunt abdominal trauma. They're particularly valuable in the instances of injuries to the spleen and kidney. What we look for on these studies is evidence of arterial displacement, occlusion, or the relatively uncommon—but quite diagnostic—arteriovenous shunting which occurs in injuries to the solid viscera. Similarly, the viscera may show displacement or actual disruption."

—ROBERT J. FREEARK, M.D., Chicago
Extracted from *Audio-Digest Surgery,* Vol. 15, No. 21, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

LETTERS *to the Editor*

Treatment of Supraventricular Tachycardia in a Child

To the Editor: One of the most common arrhythmias encountered by the pediatric cardiologist is supraventricular tachycardia, and usually it responds to digitalis and vagal stimulation. Occasionally other medications are employed—quinidine, dilantin, sometimes electric countershock and, more recently, propanolol. In a patient we treated, although propanolol diminished the frequency of attacks of supraventricular tachycardia, the quickest means of converting to normal sinus rhythm was a blow on the chest.

Report of a Case

A ten-year-old Negro girl had an initial episode of supraventricular tachycardia at six months of age. When she was digitalized, the rate slowed to normal for her age. When tachycardia recurred at 18 months, she was again digitalized, with good results.

During the next eight years, the patient complained many times of rapid heart beat but had no difficulty. In April 1968 she complained of palpitations for a three-day period, and a pediatrician found her to be in cardiac failure. Her heart rate on 16 April was 190 with inverted P waves in a number of leads of the electrocardiogram, and an x-ray film of the chest showed significant cardiomegaly. When she was treated with digitalis, the pulse rate fell to 140, and the heart became smaller. However, on 18 April an electrocardiogram showed a rate of 140 and the same inverted P waves.

Digoxin, 0.125 mg tid (0.01 mg/kg/day) and quinidine 100 mg every 2 hours X 5 on several successive days, other vagal stimulations and local carotid manipulations for hours at a time did not bring about conversion to normal sinus rhythm. Because she was otherwise well and the heart size was within normal limits, she was sent home and maintained on digoxin 0.125 mg three times a day and quinidine 50 mg three times a day.

Three months later, in July 1968, the patient was admitted to the hospital for evaluation of the use of propanolol (Inderal®). She was given a trial dose of 5 mg orally and within three hours the pulse converted to normal sinus rhythm; however, within another hour ectopic rhythm recurred. Inderal (10 mg every six hours) as well as quinidine (200 mg three times a day) did not produce normal sinus rhythm.

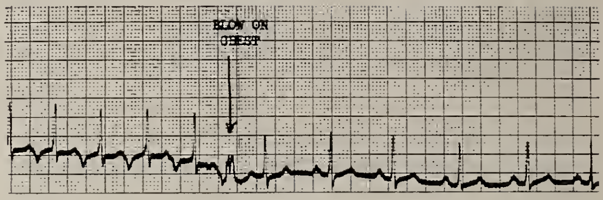

Figure 1.—Showing conversion from supraventricular tachycardia to regular sinus rhythm when patient's chest was thumped smartly over second interspace at left sternal border.

I thumped her chest smartly with my finger tips while she was having ectopic beats and noted, on the monitor, immediate conversion to sinus rhythm. When reversion to supraventricular tachycardia recurred again, I asked her to strike herself over the second interspace, left sternal border and, again, conversion occurred instantly (Figure 1). Since then, this ten-year-old girl has continued to convert supraventricular tachycardia to normal with one or two quick blows on her chest, without any discomfort. This blow-on-the-chest conversion shortens the period of arrhythmia abruptly and, once converted, the rhythm stays normal for several hours. Her current medication is propanolol 10 mg three times and quinidine 200 mg three times a day.

The precise mechanism for this conversion has yet to be elucidated. It is probably not vagal. In this patient, for example, carotid sinus stimulation did little to bring about conversion, even when she was receiving propanolol and quinidine. It does not seem to be related to fear or pain, because the blow to bring about conversion is self-administered and produces no injury. It may be an idiosyncrasy limited to this patient.

It would be of interest to know if other cardiologists have attempted cardioversion of supraventricular or other arrhythmias in a child by a blow on the chest.

MARVIN L. AUERBACK, M.D.
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Information

Coronary Arteriography

HARVEY G. KEMP, M.D., AND
RICHARD GORLIN, M.D.

Material supplied by the California Heart Association

OPACIFICATION OF THE coronary vascular system by contrast material during cardiac catheterization has had an enormous impact on our knowledge of coronary heart disease. It has allowed us, with surprising safety, to define precisely the anatomic extent of coronary atherosclerosis in living man. Added impetus has been given to coronary arteriography by new directions in therapy. For example, there is accumulating evidence that surgical revascularization of the myocardium is not only feasible but beneficial. The normal course of a recently developed diagnostic procedure, like a new drug, is to oscillate between crests of over-enthusiasm and nadirs of total rejection. Now, after some ten years, it is useful to reassess the place of coronary arteriography in the diagnostic armamentarium.

Because this article is intended to give a general view of the field to the practicing internist, surgeon, and general practitioner, relatively little attention will be given to the technical details of obtaining high quality coronary arteriography. It will be repeatedly stressed, however, that only high quality studies provide the accurate information which justifies exposing the patient to the potential hazards of the procedure.

Historical account. The two methods which have received widest application are the retrograde approach from the right brachial artery and the percutaneous retrograde approach from the femoral artery using a pre-formed catheter. In experienced hands, either of these methods can yield excellent selective studies, at low risk to the patient.

Safety. The decision to perform coronary arteriography should be based upon the weighing of the benefits expected to accrue from the resulting information, as opposed to the potential hazards involved. The latter have recently been evaluated in a cooperative study of sixteen laboratories. A total of 3,312 studies performed on 3,264 patients were included in the study group. Sixty-six complications occurred in 62 patients, for an overall complication rate of 1.9 percent. Cardiac complications occurred in ten: myocardial infarction in five, coronary insufficiency in four, and dissection of a coronary arterial wall without myocardial infarction in one. Death occurred in two of the five patients sustaining a myocardial infarction. One of these patients had an aortic valve replacement with a Starr-Edwards prosthesis, and the infarction was secondary to coronary embolism. An additional death occurred in a patient with combined coronary heart disease and aortic stenosis, yielding an overall mortality rate of less than 0.001 percent. Ventricular fibrillation occurred in 27 patients: it was found to be a more frequent complication in women, and occurred oftener after injection of the right than the left coronary artery. In each instance, the patient recovered without sequellae, indicating the relatively innocuous nature of this arrhythmia when well-trained personnel and adequate resuscitative equipment are available. Thrombosis of the brachial artery occurred in ten patients, but in the present authors' experience, this probably underestimates this complication. Fortunately if the brachial artery remains patent above the antecubital space, symptoms are slight and transient, and surgical repair is not necessary. However, surgical intervention has been necessary in about .05 percent (two of over 400) patients in the authors' experience. In both instances, surgery restored the patency of the brachial artery.

It seems reasonable to conclude from available data that the risk of death related to coronary arteriography is related to the severity of the coronary heart disease, and that significant aortic stenosis or prosthetic replacement of the aortic valve add to that risk. On the other hand, the vast majority of patients undergoing this procedure have extensive coronary disease and withstand the arteriographic study with no complication at all.

Indications. It is somewhat easier to quantify the potential hazards associated with coronary arteriography than to assess the potential benefit to the individual patient obtained from the information yielded by the procedure.

It is safe to generalize that the physician caring for a patient is always better equipped to do so when his knowledge of the patient's condition is

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Junior Associate in Medicine, Peter Bent Brigham Hospital and Instructor in Medicine, Harvard Medical School, Boston (Kemp); Director, Cardiovascular Unit and Physician, Peter Bent Brigham Hospital and Assistant Professor of Medicine, Harvard Medical School, Boston (Gorlin).

extended. This is particularly true of diseases in which there is relatively poor correlation between symptoms, indirect measurements, and the extent of anatomic disease. In this regard, several specific observations about coronary heart disease have emphasized the usefulness of arteriography. Studies in the past based solely on autopsy material had shown an excellent correlation between a clinical history of angina pectoris and extensive coronary atherosclerosis. Since the advent of coronary arteriography, however, a group of patients has emerged with angina pectoris but whose major coronary arteries are free of intraluminal obstruction. The incidence of this paradoxical syndrome has been consistently reported to be about 10 percent of subjects referred to centers performing coronary arteriography because of angina pectoris. The etiology of angina in this group remains obscure, but it would seem probable that the appropriate treatment and prognosis of this group will prove to be significantly different from their counterparts with arteriographically demonstrable coronary atherosclerosis. At present, there are no methods other than arteriography to differentiate these two groups.

In addition to the unusual syndrome just described, there are many patients with less typical histories, with non-specific electrocardiographic abnormalities, with unexplained congestive heart failure, arrhythmia or some combination of the above, in whom coronary heart disease is suspected but cannot be included or excluded on clinical grounds alone. An unknown, but certainly high, percentage of these patients will have normal coronary arteriograms and treatment can be redirected, either toward correction of whatever disease is found, or, in the absence of demonstrable heart disease, toward psychologic rehabilitation. The amount of psychologic damage done to patients by well-intentioned physicians who have erroneously attached the label of coronary heart disease to some masquerading symptom complex, can neither be overestimated nor readily undone.

Perhaps the largest group of patients who merit coronary arteriographic studies includes those who have clearly established coronary heart disease associated with chest pain syndromes not easily controlled by medical management. It is obvious that several value judgments are called for in including the individual patient in this group, and that probably no two observers would consistently evaluate the same patient in exactly the same fashion. Also, it is clear that while the results of myocardial revascularization are being more precisely defined in terms of pain relief, objective signs of increased myocardial perfusion, and longevity, our criteria for study will continue to change. Although it is not within the scope of this report to critically evaluate the status of myocardial revascularization, the threshold for a decision to obtain arteriographic studies is inextricably related to one's evaluation of the benefits potentially available through surgical intervention. Addressing ourselves to this specific point, the authors believe that present data strongly indicate that not only can pain syndromes be substantially relieved by internal mammary artery implantation, but that there is objective evidence of improved myocardial perfusion and further that there is reason for optimism concerning improvement in longevity, particularly in patients surviving 18 months after the procedure. In addition, new revascularization procedures, particularly the direct replacement of segments of the right coronary artery with venous grafts, currently show promise. As surgical procedures have continued to evolve, young patients with myocardial infarction without pain or congestive heart failure have become legitimate subjects for arteriography, at least in centers where data concerning the effect of revascularization on longevity are being actively accrued and evaluated. For the present, it seems unwise and overly conservative to allow patients to severely restrict their lives because of coronary heart disease, and this is particularly true of the young patient.

There are a number of miscellaneous indications for coronary arteriography. Patients with angina and aortic valve disease being considered for valvular replacement should certainly be studied and probably patients with mitral valve disease as well. This enables the cardiologist to better understand total myocardial function and make a more objective estimate of surgical risk and ultimate prognosis. It provides very helpful information for the surgeons who will be perfusing the coronaries at the time of surgery. Uncommon specific indications for coronary arteriography include suspected congenital malformations, luetic involvement of the coronary ostia, and coronary artery embolism.

To some degree, the indication for adding selective coronary arteriography to any retrograde left heart catheterization procedure performed on a patient in the coronary age group depends upon the ease with which the particular laboratory can perform coronary arteriography. If experienced personnel are available, it can add very helpful information at a negligible additional risk to the patient. Left heart catheterization of a patient with suspected cardiomyopathy is an excellent case in point.

Accuracy of coronary arteriography. Every diagnostic procedure must be evaluated in the light of the accuracy of the information it yields. When one views coronary arteriography of excellent radiographic quality, a highly accurate picture of the major coronary vessels and their branches has been obtained. A study comparing the interpretation of coronary arteriography with the actual amount of disease found at necropsy done on 29 subjects at the Peter Bent Brigham Hospital confirmed this impression. Of the many opportunities for error in interpreting 145 coronary arteries individually, only three errors of functional significance were made. There was a direct relationship between the accuracy of interpretation and the radiographic quality of the arteriography, significant errors being made only in films of borderline quality.

A number of factors contribute to radiographic quality, most of which are of technical nature and are not germane to the present discussion. It is sufficient to remember that appropriate magnification, contrast, focus, and day-to-day consistency are essential and most often found in a laboratory with a high degree of interest in an almost daily use of coronary arteriography.

THE SUDDEN DEATH SYNDROME IN BABIES

"[On the basis of a three-year study,] we are saying that the sudden death syndrome can no longer exist in the 'mystery-killer' category. It's a real disease; it has *real* clinical and pathological findings. The clinical findings are a child between the ages of two weeks and eight months who is found dead. The pathological findings are pulmonary congestion, intrathoracic petechiae, pharyngeal inflammation, fluid blood, and an empty bladder. We're saying that this is a definite disease and should be called as a definite disease.

"Even though he cannot predict or prevent sudden death syndrome at this time, the physician has a most important role. He must recognize that the sudden death syndrome is a disease, and that most parents feel that they have been responsible for their child's death. He must work to allay their guilt. . . .

"Most parents think their baby suffocated. We tell them his death was not due to suffocation. We tell them that this is a definite disease; that they weren't responsible; and that it's just like a bolt of lightning—there was no way to predict or prevent it. We have to tell them this repeatedly and tell it to their families, to children, and to grandparents, so they don't suffer the tragic psychiatric consequences of feeling the rest of their lives that they killed their child. We also tell the parents that this should not prevent them from having other children; chances are something like 499 out of 500 that their next child is going to be great."

—ABRAHAM B. BERGMAN, M.D., Seattle

Extracted from *Audio-Digest Pediatrics,* Vol. 14, No. 21, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

Reports of officers of the California Medical Association, together with the detailed audited financial statements for the fiscal year ended June 30, 1968, heretofore published annually in California Medicine, are being printed this year only in the Annual Reports Bulletin. The Bulletin, which is distributed to Delegates and Alternates at the meeting of the House of Delegates, is also available to any member of the Association on request directed to Lytton O. Hetland, Director of Financial Affairs, California Medical Association, 693 Sutter Street, San Francisco, California 94102.

REPORT OF
Certified Public Accountants

California Medical Association:

We have examined the balance sheets of California Medical Association and Trustees of California Medical Association at June 30, 1968, and the related statements of income and expenses for the year then ended. Our examinations were made in accordance with generally accepted auditing standards, and accordingly included such tests of the accounting records and such other auditing procedures as we considered necessary in the circumstances.

In our opinion, the statements referred to above present fairly the financial position of California Medical Association and Trustees of California Medical Association at June 30, 1968, and the results of their operations for the year then ended, in conformity with generally accepted accounting principles applied on a basis consistent with that of the preceding year.

John F. Forbes & Company

San Francisco, California
August 8, 1968

FINANCIAL REPORTS

CALIFORNIA MEDICAL ASSOCIATION AND AFFILIATED COMPANIES

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Trustees of the California Medical Association:

Exhibit C—Balance Sheet, June 30, 1968 and 1967, and Comparison
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California Medical Association and
Trustees of the California Medical Association:

Notes to Financial Statements, June 30, 1968

CALIFORNIA MEDICAL ASSOCIATION

(A Nonprofit Association)

Balance Sheet June 30, 1968 and 1967 and Comparison

	JUNE 30 1968	JUNE 30 1967	Increase (Decrease)
ASSETS			
CASH	$ 93,963	$ 71,474	$ 22,489
CERTIFICATE OF DEPOSIT— CROCKER-CITIZENS NATIONAL BANK	500,000	1,000,000	*(500,000)*
UNITED STATES TREASURY BILLS, AT COST	493,497		493,497
ACCOUNTS RECEIVABLE, NET	77,740	81,990	*(4,250)*
ACCRUED INTEREST	3,995	9,409	*(5,414)*
NOTES RECEIVABLE:			
Central California Blood Bank	71,000	71,000	
Other	4,000		4,000
	75,000	71,000	4,000
PREPAID EXPENSES AND OTHER ASSETS:			
Retirement program premium (Note 1)	19,054	18,204	850
Insurance	3,218	4,398	*(1,180)*
Deposits	3,549	1,834	1,715
Other	1,224	1,372	*(148)*
Total prepaid expenses and other assets	27,045	25,808	1,237
OFFICE FURNITURE AND EQUIPMENT (Note 2)	34,439	23,125	11,314
NOTE AND ACCOUNTS RECEIVABLE, AFFILIATED ORGANIZATIONS:			
Trustees of the California Medical Association:			
Demand note, with interest at 4% per year	125,000		125,000
Account receivable	2,170	18	2,152
	127,170	18	127,152
Accounts receivable:			
Six Ninety Three Sutter Publications, Inc.	3,470		3,470
California Medical Education and Research Foundation, Inc.	2,887	20,622	*(17,735)*
California Committee on Regional Medical Programs	550		550
Total note and accounts receivable, affiliated organizations	134,077	20,640	113,437
	$1,439,756	$1,303,446	$ 136,310
LIABILITIES			
ACCOUNTS PAYABLE:			
American Medical Education Foundation	$ 81,688	$ 108,228	$ *(26,540)*
Other	90,757	105,466	*(14,709)*
Total accounts payable	172,445	213,694	*(41,249)*
DEFERRED INCOME:			
Dues and subscriptions applicable to the succeeding fiscal year	917,196	894,783	22,413
Other	863	4,230	*(3,367)*
Total deferred income	918,059	899,013	19,046
DUE TO AFFILIATED ORGANIZATIONS:			
Physicians' Benevolence Fund		23,077	*(23,077)*
Six Ninety Three Sutter Publications		10,452	*(10,452)*
Total due to affiliated organizations		33,529	*(33,529)*
EXCESS OF ASSETS OVER LIABILITIES (Note 3):			
Restricted as to use (Note 4)	115,721		115,721
Unrestricted:			
Balance at beginning of year	157,210	33,712	123,498
Excess of income over expenses for the year	192,042	123,498	68,544
Transfer to restricted balance	*(115,721)*		*(115,721)*
Balance at end of year	233,531	157,210	76,321
Total excess of assets over liabilities	349,252	157,210	192,042
	$1,439,756	$1,303,446	$ 136,310

See notes to financial statements.

CALIFORNIA MEDICAL ASSOCIATION

Statement of Income and Expenses Years Ended June 30, 1968 and 1967 and Comparison

	YEAR ENDED JUNE 30		Increase (Decrease)
	1968	1967	
INCOME:			
Membership dues, less portion allocated to California Medicine subscriptions	$1,869,948	$1,669,828	$ 200,120
Booth rentals at annual session	37,930	40,935	*(3,005)*
Postgraduate fees	14,406	15,363	*(957)*
Interest earned	21,257	20,483	774
Other	15,330	16,217	*(887)*
	1,958,871	1,762,826	196,045
EXPENSES:			
Operational	410,503	387,640	22,863
Scientific, educational, and communications	751,334	800,941	*(49,607)*
Contributions	136,525	185,008	*(48,483)*
Physicians' services and programs	319,647	265,739	53,908
Field services	148,820		148,820
	1,766,829	1,639,328	127,501
EXCESS OF INCOME OVER EXPENSES FOR THE YEAR	$ 192,042	$ 123,498	$ 68,544

See notes to financial statements.

TRUSTEES OF THE CALIFORNIA MEDICAL ASSOCIATION

Statement of Income and Expenses Years Ended June 30, 1968 and 1967 and Comparison

	YEAR ENDED JUNE 30		Increase (Decrease)
	1968	1967	
INCOME:			
Excess of rental income over property expenses (property expenses over rental income)	$13,833	$ *(7,910)*	$21,743
Interest on United States Treasury bonds and bills	29,000	29,278	*(278)*
Dividend—Pacific Magnetic Tape Equipment Co.	900	900	
Miscellaneous	52	52	
	43,785	22,320	21,465
EXPENSES (other than property)—Fees and insurance	2,736	4,308	*(1,572)*
	41,049	18,012	23,037
OTHER CHARGES:			
Net premium on life and retirement insurance policy	3,853	4,053	*(200)*
Provision for retirement or other benefit of an employee of an affiliated organization	3,111	3,000	111
Provision for deferred compensation	3,000	3,000	
	9,964	10,053	*(89)*
EXCESS OF INCOME OVER EXPENSES FOR THE YEAR	$31,085	$ 7,959	$23,126

See notes to financial statements.

TRUSTEES OF THE CALIFORNIA MEDICAL ASSOCIATION

(A Nonprofit Corporation)

Balance Sheet June 30, 1968 and 1967 and Comparison

	JUNE 30		Increase (Decrease)
	1968	1967	
ASSETS			
CASH	$ 25,701	$ 24,423	$ 1,278
UNITED STATES TREASURY BONDS, AT COST (maturity value, $1,121,000; market value, 1968, $1,014,616 and 1967, $1,001,072)	1,119,152	1,119,152	
NOTE AND ACCOUNTS RECEIVABLE	6,017	2,850	3,167
ACCRUED INTEREST ON SECURITIES	2,119	2,119	
INVESTMENTS IN WHOLLY-OWNED SUBSIDIARIES, AT COST:			
Pacific Magnetic Tape Co. (Note 5)	9,000	9,000	
Six Ninety Three Sutter Publications, Inc.	1,000	1,000	
Total investments in wholly-owned subsidiaries	10,000	10,000	
PROPERTIES, AT COST (Note 6):			
Land	180,217	180,217	
Buildings and improvements	392,800	378,383	14,417
Furniture and equipment	8,575	5,198	3,377
	581,592	563,798	17,794
Less accumulated depreciation	99,501	83,685	15,816
Properties, net	482,091	480,113	1,978
EQUIPMENT, AT NOMINAL VALUE	1	1	
CASH SURRENDER VALUE OF LIFE INSURANCE	46,080	40,838	5,242
PREPAID INSURANCE	1,458	3,800	*(2,342)*
REAL ESTATE TAXES APPLICABLE TO SUBSEQUENT YEAR (contra)	16,700	19,000	*(2,300)*
	$1,709,319	$1,702,296	$ 7,023
LIABILITIES			
ACCOUNTS PAYABLE AND ACCRUED EXPENSES:			
California Medical Association	$ 1,319	$ 17	$ 1,302
Interest and accrued expenses	3,004	2,408	596
Real estate taxes (contra)	16,700	19,000	*(2,300)*
Total accounts payable and accrued expenses	21,023	21,425	*(402)*
NOTES PAYABLE:			
California Medical Association, payable on demand, with interest at 4% per year—Unsecured	125,000		125,000
The Connecticut Mutual Life Insurance Company, with deed of trust as collateral (payable in quarterly installments of $2,506, including interest, to March 1, 1973) (Note 6)	40,452	48,541	*(8,089)*
Crocker-Citizens National Bank—Unsecured		150,000	*(150,000)*
Total notes payable	165,452	198,541	*(33,089)*
TRUST FUNDS (Note 7)	125,127	115,789	9,338
DEFERRED COMPENSATION PAYABLE	16,750	16,500	250
DEFERRED INCOME	753	912	*(159)*
EXCESS OF ASSETS OVER LIABILITIES (Note 3):			
Balance at beginning of year	1,349,129	1,341,170	7,959
Excess of income over expenses for the year	31,085	7,959	23,126
Balance at end of year	1,380,214	1,349,129	31,085
	$1,709,319	$1,702,296	$ 7,023

See notes to financial statements.

CALIFORNIA MEDICAL ASSOCIATION and TRUSTEES OF THE CALIFORNIA MEDICAL ASSOCIATION

Notes to Financial Statements June 30, 1968

NOTE:

1. EMPLOYEE PENSION PLANS

In addition to the Group Pension Program which became effective on January 1, 1961, the California Medical Association has arranged for the funding of a Past Service Pension Plan for certain full-time employees. The previously required waiting period of three years was eliminated, which resulted in an additional liability of $62,734. This liability will be amortized over 20 years. The Travelers' Insurance Company has underwritten the plan and will furnish annuity contracts as eligible employees retire. Neither the amount on deposit nor any liability for pensions is carried on the books of the Association or included in the accompanying balance sheet. The plan is on a calendar-year basis.

The net pension expense for the year was $23,892 which includes amortization of prior service costs over a period of 20 years. It is the policy of the Association to fund pension costs as accrued. The actuarially computed value of vested benefits at June 30, 1968 exceeded the total of the pension fund less pension prepayments by approximately $10,060.

2. OFFICE FURNITURE AND EQUIPMENT

Acquisitions prior to July 1, 1966 are carried at a nominal amount of $1. At May 13, 1966, the firm of Marshall and Stevens, appraisers, estimated that the sound value of assets then owned was $104,415. Assets acquired after July 1, 1966, are summarized as follows:

	Cost	Depreciation or Amortization
Office furniture and equipment:		
Owned July 1, 1967	$25,385	$2,533
Purchased during the current year	14,217	
Provision for the current year		5,691
	39,602	8,224
Leasehold improvements, Sacramento office:		
Cost	3,357	
Amortization		296
	$42,959	$8,520
Net book value	$34,439	

3. COMBINED NET WORTH

The Trustees of the California Medical Association is a wholly-owned subsidiary of the California Medical Association. The Trustees hold in trust a large portion of the assets utilized by the California Medical Association. The combined net worth of the two organizations is summarized as follows:

Entity	JUNE 30 1968	1967	Increase
California Medical Association:			
Restricted as to use	$ 115,721		$115,721
Unrestricted	233,531	$ 157,210	76,321
	349,252	157,210	192,042
Trustees of the California Medical Association	1,380,214	1,349,129	31,085
	$1,729,466	$1,506,339	$223,127

The combined net worth at June 30, 1968 shown in the summary above does not include the following items:

California Medical Association:	
Excess of the appraised value of furniture and office equipment acquired prior to July 1, 1966 over accumulated depreciation and nominal carrying value, approximately	$ 83,000
Audio-Digest Foundation, a wholly-owned subsidiary; net worth as shown by the Foundation's audited balance sheet at June 30, 1968	328,603
	411,603
Trustees of the California Medical Association—Excess of net worth over Trustees' investment in their wholly-owned subsidiary, Pacific Magnetic Tape Co., based on that company's unaudited balance sheet at June 27, 1968	36,337
	$447,940

4. EXCESS OF ASSETS OVER LIABILITIES—RESTRICTED AS TO USE

The budget for the fiscal year ended June 30, 1968, as approved by the Council, authorized the segregation of a portion of the excess of income over expenses in the amount of $115,721, leaving the remainder available for possible current requirements.

5. WHOLLY-OWNED SUBSIDIARY

The Trustees of the California Medical Association owns all of the outstanding stock of the Pacific Magnetic Tape Equipment Co., which was formed for the purpose of merchandising magnetic tape equipment as an adjunct to the activities of the Audio-Digest Foundation, a wholly-owned subsidiary of the California Medical Association.

6. PROPERTIES

On October 10, 1966, the Trustees of the California Medical Association purchased the land and building located at 679 Sutter Street. The properties are summarized as follows:

	693 Sutter Street	679 Sutter Street	Total
Land	$ 87,400	$ 92,817	$180,217
Buildings and improvements	314,911	77,889	392,800
Furniture and equipment	8,575		8,575
	410,886	170,706	581,592
Less accumulated depreciation	92,848	6,653	99,501
	$318,038	$164,053	$482,091

The property located at 693 Sutter Street, San Francisco, is subject to a deed of trust to The Connecticut Mutual Life Insurance Company as collateral for a note with a balance of $40,452 at June 30, 1968.

7. TRUST FUNDS

These funds are summarized as follows:

For Mr. and Mrs. Ben H. Read	$ 60,000
Morris Herzstein Bequest	19,047
Life insurance retirement plan for legal counsel	46,080
	$125,127

The portion of the Trust Funds applicable to the retirement or similar benefit to Mr. and Mrs. Ben H. Read, has not been segregated from other assets of the corporation as provided by the bylaws, as such funds are presently invested in United States Treasury securities of indivisible denominations.

The life insurance retirement plan for legal counsel is offset by the cash surrender value of a life insurance policy.

In Memoriam

Bennett, Charles Barrows, Berkeley. Died 7 January 1969 of acute myocardial infarction, aged 87. Graduate of University of California Medical School, Berkeley-San Francisco, 1918. Licensed in California in 1918. Doctor Bennett was a member of the Alameda-Contra Costa Medical Association.

◆

Bergmann, John Elmer, Santa Monica. Died 12 January 1969 in Palm Springs, aged 68. Graduate of University of Cincinnati College of Medicine, Cincinnati, 1925. Licensed in California in 1932. Doctor Bergmann was a member of the Los Angeles County Medical Association.

◆

Bloss, Andrew M., Hollydale. Died 8 January 1969 in South Gate of insulin shock due to diabetes mellitus, aged 53. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1943. Licensed in California in 1943. M.D. degree from California College of Medicine, 1962. Doctor Bloss was a member of the Los Angeles County Medical Association.

◆

Butka, Leslie Harrison, La Verne. Died 10 January 1969 in La Verne of injuries sustained in an automobile accident, aged 78. Graduate of College of Medical Evangelists, Los Angeles, 1916. Licensed in California in 1916. Doctor Butka was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

◆

Cass, Alonzo Beecher, Los Angeles. Died 2 February 1969 in San Francisco, aged 62. Graduate of Stanford University School of Medicine, Palo Alto and San Francisco, 1935. Licensed in California in 1935. Doctor Cass was an associate member of the Los Angeles County Medical Association.

◆

Coblentz, Zach Benjamin, San Francisco. Died 23 January 1969 in San Francisco of heart disease, aged 75. Graduate of University of California Medical School, San Francisco, 1921. Licensed in California in 1921. Doctor Coblentz was an associate member of the San Francisco Medical Society.

◆

Durkee, Carleton Fabian, Los Angeles. Died 30 January 1969 in Los Angeles of acute circulatory failure, aged 60. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1948. Licensed in California in 1948. M.D. degree from California College of Medicine, Los Angeles, 1962. Doctor Durkee was a member of the Los Angeles County Medical Association.

Edwards, Henry W., Arcadia. Died 27 January 1969 in Arcadia of pneumonia, aged 95. Graduate of Bellevue Hospital Medical College, New York City, 1897. Licensed in California in 1913. Doctor Edwards was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

◆

Ellis, Ving, Walnut Creek. Died 16 January 1969 in Walnut Creek of carcinoma of the rectum, aged 56. Graduate of University of California School of Medicine, Berkeley-San Francisco, 1950. Licensed in California in 1950. Doctor Ellis was a member of the Alameda-Contra Costa Medical Association.

◆

Farman, G. Franklin, Lakewood. Died 27 January 1969 in Long Beach of congestive heart failure, aged 76. Graduate of Rush Medical College, Chicago, 1917. Licensed in California in 1921. Doctor Farman was a member of the Los Angeles County Medical Association.

◆

Grisdale, Clarence John Milton, Glendale. Died 27 January 1969 in Glendale of heart disease, aged 53. Graduate of McGill University Faculty of Medicine, Montreal, 1941. Licensed in California in 1956. Doctor Grisdale was a member of the Los Angeles County Medical Association.

◆

Hand, Mark Melchus, San Francisco. Died 26 January 1969 in San Francisco, aged 63. Graduate of The Creighton University School of Medicine, Omaha, 1931. Licensed in California in 1931. Doctor Hand was a member of the San Francisco Medical Society.

◆

Hara, Margaret Elisabeth Farr, Los Angeles. Died 9 January 1969 in Los Angeles of cerebral vascular accident, aged 80. Graduate of The Hahnemann Medical College and Hospital, Chicago, 1914. Licensed in California in 1917. Doctor Hara was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

◆

Klein, Henry Lipscomb, Castro Valley. Died 24 December 1968 of arteriosclerotic heart disease, aged 72. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1918. Licensed in California in 1949. Doctor Klein was a member of the Butte-Glenn Medical Society.

Klug, Albert B., San Diego. Died 18 January 1969 of cancer, aged 45. Graduate of University of Michigan Medical School, Ann Arbor, 1949. Licensed in California in 1950. Doctor Klug was a member of the San Diego Medical Society.

⁂

Le Blond, Harold D., Long Beach. Died 29 January 1969 in Los Angeles following open heart surgery, aged 58. Graduate of University of Michigan Medical School, Ann Arbor, 1938. Licensed in California in 1947. Doctor LeBlond was a member of the Los Angeles County Medical Association.

⁂

Lee, David, Downey. Died 16 January 1969 in Santa Monica of pneumonia, aged 57. Graduate of University of Southern California School of Medicine, Los Angeles, 1950. Licensed in California in 1950. Doctor Lee was a member of the Los Angeles County Medical Association.

⁂

Maclean, J. Alexander, Baldwin, Kansas. Died December 1968 in Chanute, Kansas, of pulmonary tuberculosis, aged 65. Graduate of University of Kansas School of Medicine, Lawrence-Kansas City, 1939. Licensed in California in 1944. Doctor Maclean was a member of the Los Angeles County Medical Association.

⁂

Mahoney, Louis E., Santa Monica. Died 25 January 1969 in Santa Monica of cardiac decompensation, aged 74. Graduate of University of Colorado School of Medicine, Denver, 1922. Licensed in California in 1923. Doctor Mahoney was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

⁂

Manuel, Madeline Marlowe, Los Angeles. Died 4 December 1968 in Laguna Beach of heart disease, aged 70. Graduate of University of California Medical School, San Francisco, 1925. Licensed in California in 1925. Doctor Manuel was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

Mathes, Mary Elizabeth, San Francisco. Died 10 January 1969 in San Francisco of pneumonia, aged 70. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1928. Licensed in California in 1928. Doctor Mathes was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

⁂

Noble, Thomas Elwood, Long Beach. Died 6 January 1969 in Long Beach of pneumonia, aged 69. Graduate of University of Minnesota Medical School, Minneapolis, 1924. Licensed in California in 1925. Doctor Noble was a member of the Los Angeles County Medical Association.

⁂

Silverthorn, John Roy, Downey. Died 7 December 1968 in Downey of renal failure and nephrosclerosis, aged 90. Graduate of Hospital College of Medicine, Louisville, Ky., 1901. Licensed in California in 1917. Doctor Silverthorn was a member of the Los Angeles County Medical Association.

⁂

Valentine, Linville Franklin, Los Angeles. Died 16 January 1969 in Culver City of carcinoma of the liver, aged 66. Graduate of University of Nebraska College of Medicine, Omaha, 1928. Licensed in California in 1953. Doctor Valentine was a member of the Los Angeles County Medical Association.

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H., Director, State Department of Public Health

Recent Health Legislation

THE 1968 REGULAR SESSION of the State Legislature acted on a number of public health and medical bills. Summarized, here are a few of them of interest to physicians:

Three measures relate to **medical services to minors.**

Perhaps the most significant of these is Assembly Bill 656 (Sec. 34.7, Civil Code) which permits a minor 12 years of age or older who may have had contact with a reportable communicable disease to give consent for hospital, medical or surgical care related to the condition.

This statute will **help to control venereal diseases,** since a significant proportion of these infections occur in minors. The statute facilitates speedy treatment when parental consent cannot be readily obtained.

Assembly Bill 334 (Sec. 34.6, Civil Code) permits minors 15 years of age or older, who live apart from their parents or guardians and who are managing their own financial affairs, to give consent for medical, surgical, hospital and dental care, including x-ray and anesthesia.

Senate Bill 1245 (Sec. 25.5, Civil Code) allows a minor 18 years of age or older to consent to be a blood donor and allow penetration of tissue necessary for blood collection.

There was considerable **legislative activity on drugs** during the last session.

AB 194 amends Sec. 11655 of the Health and Safety Code to set up procedures making **marijuana** more readily obtainable for research.

AB 195 gives a sum of money to the University of California to study the effects of marijuana.

AB 196 (Sec. 11395 of the Health and Safety Code) clarifies the law requiring physicians to report **treatment of patients for narcotics addiction.**

AB 979 (Sec. 11333, Health and Safety Code) sets up procedures by which "seized narcotics" may be made available to qualified persons for research.

AB 1764 amends Sec. 11166.12 of the Health and Safety Code to exempt **dihydrocodeine** when combined with other active non-narcotic ingredients from the triplicate prescription requirement.

SB 1268 amends several sections of the Health and Safety Code relating to the category of "restricted dangerous drugs" having a potential for abuse. The law establishes a Research Advisory Panel on **hallucinogenic drugs.** It also establishes procedures by which qualified persons may obtain such drugs for research under specified conditions and it continues to forbid possession of or furnishing by prescription of LSD and DMT.

A proposed law, AB 1308, would have made it mandatory for the pharmacist to label a prescribed drug for the patient's information, unless the physician specifically asked the pharmacist not to do so. The bill was not passed, but was referred to the Board of Pharmacy, which will consider adopting such a requirement as a regulation.

The Board of Pharmacy and the Board of Medical Examiners have clarified the ruling that only a physician may prescribe for a patient. A nurse may not transmit a prescription either to patient or to pharmacist. Careful observation of this law may help to solve the serious **problem of forged prescriptions.**

Assembly Bill 137 amends Sections 11110 and 11161.5 of the Penal Code in several details. Physicians will recall that this **"battered child" statute** requires physicians and surgeons, including residents and interns, to report physical injuries which appear to have been inflicted on a minor by other than accidental means. The amendments assure that the physician will not incur any civil or criminal liability as a consequence of reporting.

AB 859 exempts physicians, among others, from civil or criminal liability as a result of "proper administering of a blood test" for **alcohol determination** when it is requested in writing by a peace officer.

SB 912 (Sec. 651.2, Business and Professions Code) makes it unlawful for any person licensed under provisions relating to the healing arts, to advertise that he will furnish any commodity or service free in connection with his professional practice or business.

AB 1413 allocates to the State Department of Public Health a sum of money to establish and maintain a three-year pilot program for diagnosis and treatment of children suffering from **hyaline membrane disease.**

EDUCATION NOTICES

Meetings and Courses

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of the dates of continuing education programs and the meetings of various medical organizations in California is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102; or phone: (415) 776-9400, extension 241.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts
for Postgraduate Course Information

CMA:	**California Medical Association** For information contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. (415) 776-9400, ext. 241.
LLU:	**Loma Linda University** For information contact: John E. Peterson, M.D., Associate Dean for Research Affairs, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.
PMC:	**Pacific Medical Center** For information contact: Arthur Selzer, M.D., Chairman, Education Committee, Pacific Medical Center, Clay and Webster Streets, San Francisco 94115. (415) 931-8000.
STAN:	**Stanford University** For information contact: Thomas A. Gonda, M.D., Associate Dean, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5940.
UCD:	**University of California, Davis** For information contact: Charles J. Tupper, M.D., Dean, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0333.
UCI:	**University of California — California College of Medicine, Irvine** For information contact: Robert Combs, M.D., Associate Dean, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.
UCLA:	**University of California, Los Angeles** For information contact: Donald Brayton, M.D., Associate Dean and Head, Continuing Education in Medicine and the Health Sciences, 15-39 Rehabilitation Center, UCLA Center for the Health Sciences, Los Angeles 90024. (213) 825-6514.
UCSD:	**University of California, San Diego** For information contact: Clifford Grobstein, Ph.D., Dean, University of California, San Diego, School of Medicine, La Jolla 92038. (714) 453-2000.
UCSF:	**University of California, San Francisco** For information contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, Health Sciences, University of California Medical Center, San Francisco 94122. (415) 666-1692.
USC:	**University of Southern California** For information contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 225-1511, ext. 203.

APRIL

April 2—**Office Dermatology.** PMC. Wednesday.

April 2—**Clinical Uses of Isotopes.** PMC. Wednesday.

April 5-6—**Pediatric Allergy.** PMC. Saturday-Sunday.

April 7-16 — **Cardiology for the Consultant.** Rancho Santa Fe Inn, San Diego. Two weeks. Contact: William D. Nelligan, Executive Director, American College of Cardiology, 9650 Rockville Pike, Rockville, Maryland 20014.

April 8-9—**American Association of Planned Parenthood Physicians.** St. Francis Hotel, San Francisco. Tuesday-Wednesday. Contact: Planned Parenthood, World Population, 515 Madison Avenue, New York 10022.

April 9-June 11—**Group Methods.** UCSF at VA Hospital, San Francisco. Wednesdays.

April 10-11—**General Surgery.** UCSF. Thursday-Friday.

April 10-12—**Current Concepts and Practice of Obstetrical Anesthesia.** UCSF. Thursday-Saturday. $75.

April 10-12 — **Western Electroencephalography Society.** Anaheim. Thursday-Saturday. Contact: E. E. Shev, M.D., 516 Sutter Street, Suite 812, San Francisco 94102.

April 11-12 — **Annual Symposium on Cardiovascular Diseases.** Sacramento-Yolo-Sierra Heart Association at Sacramento Inn, Sacramento. Friday-Saturday. Contact: Malcolm M. McHenry, M.D., Cardiopulmonary Laboratory, Sutter Memorial Hospital, 52nd and F Streets, Sacramento 95819. (916) 452-3271, extension 479.

April 11-12—**Vascular Surgery.** USC at Statler Hilton Hotel, Los Angeles. Friday-Saturday.

April 11-12—**14th Annual Pediatric Symposium.** Ambassador Hotel, Los Angeles. Southern California Permanente Medical Group and Kaiser Foundation Hospitals. Friday-Saturday. Contact: Mrs. Shirley Gach, 4900 Sunset Boulevard, Room 3007, Los Angeles 90027.

April 12—**Medical Emergencies.** UCLA. Saturday.

April 12-13—**Psychiatry Program.** UCSF at Stockton State Hospital. Saturday-Sunday.

April 12-13—**Heart Conference.** RMP Area VI at Holiday Inn, Palm Springs. Saturday-Sunday. $10. Contact: John E. Peterson, M.D., Associate Dean for Research Affairs, Loma Linda University School of Medicine, Loma Linda 92354.

April 13—**Obstetrical Emergencies.** UCLA. Sunday.

April 13-17—**Pacific Coast Oto-Ophthalmological Society.** Hilton Hotel, San Francisco. Sunday-Thursday. Contact: Francis A. Sooy, M.D., Secretary-Treasurer, Department of Otolaryngology, UC Medical Center, San Francisco 94122.

April 16—**Working with the Chinese in San Francisco.** Agnews State Hospital, San Jose. Wednesday. Contact: J. Elizabeth Jeffress, M.D., Chief of Professional Education, Agnews State Hospital, San Jose 95114.

April 17-18 — **Annual Meeting, California Thoracic Society.** El Cortez Hotel, San Diego. Thursday-Friday. Contact: William F. Roberts, Director, Public Relations Division, TB and Health Association of California, 424 Pendleton Way, Oakland 94621. (415) 636-1756.

April 17-18—**The 17th Annual Postgraduate Seminar and Clifford Sweet Memorial Lecture.** Childrens Hospital Medical Center, Oakland. Thursday-Friday. $20. Contact: Inetta Carty, Childrens Hospital Medical Center, 51st and Grove Streets, Oakland.

April 17-19—**Advances in Endocrinology and Metabolism.** UCSF. Thursday-Saturday.

April 18—**Neurological Evaluation.** PMC. Friday.

April 18 — **Spring Symposium in Heart Disease.** Orange. Friday. Contact: Janice Ayres, Orange County Heart Association, 1043 West 8th Street, Santa Ana 92703.

April 18-19—**The Stroke Symposium.** Alameda and Contra Costa County Heart Associations at Holiday Inn, Concord. Friday-Saturday. $25. Contact: Loyse C. Casebolt, Executive Director, Contra Costa County Heart Association, P.O. Box 212, Walnut Creek 94596. (415) 935-1060.

April 20 — **Medical Legal Problems: A Program for Medical Assistants.** UCSF. Sunday.

April 26—**Legal Problems as They Relate to the Medical Assistant.** Orthopaedic Hospital, Los Angeles. Saturday. Contact: UCLA.

April 26-27—**Comparative Oncology.** UCSF. Saturday-Sunday.

April 26-27—**Community Psychiatry.** UCSF. Saturday-Sunday.

April 27-29—**American Society of Maxillofacial Surgeons.** Fairmont Hotel, San Francisco. Sunday-Tuesday. Contact: Dicran Goulian, Jr., M.D., Secretary-Treasurer, 116 East 68th Street, New York 10021.

April 30 - May 3 — **American Association of Plastic Surgeons.** Fairmont Hotel, San Francisco. Wednesday-Saturday. Contact: Clarence W. Monroe, M.D., Secretary, 715 Lake Street, Oak Park, Illinois 60301.

MAY

May 2-3—**SAN JOAQUIN VALLEY COUNTIES—Regional Postgraduate Institute.** Sponsored by CMA, University of California, Irvine and San Joaquin Valley Counties Medical Societies. Friday-Saturday. 14 hours. $20. Contact: CMA.

May 2-4—**Northern California Chapter, Western Orthopedic Association.** Del Monte Lodge, Pebble Beach. Friday-Sunday. Contact: Mrs. Ida Ruth Haggerty, Executive Secretary, 3901 Ardley Avenue, Oakland 94602. (415) 533-6790.

May 3-4—**Inhalation Therapy.** UCLA. Saturday-Sunday.

May 3-4, 17-18—**Intermediate Methods in Family Therapy.** UCSF in Modesto. Two weekends.

May 5-8—**Aerospace Medical Association.** Hilton Hotel, San Francisco. Monday-Thursday. Contact: William J. Kennard, M.D., Executive Vice President, Washington National Airport, Washington, D.C. 20001.

May 5-8—**Civil Aviation Medical Association.** Hilton Hotel, San Francisco. Monday-Thursday. Contact: Charles K. Holbrook, M.D., Secretary-Treasurer, 9901 Diamond Drive, St. Louis 63137.

May 7—**Annual Meeting, Los Angeles County Heart Association.** Hilton Hotel, Los Angeles. Wednesday. Contact: Los Angeles County Heart Association, 2405 West Eighth Street, Los Angeles 90057.

May 7-9—**American Association of Genitourinary Surgeons.** Del Monte Lodge, Pebble Beach. Wednesday-Friday. Contact: Harry M. Spence, M.D., Executive Secretary, 4105 Live Oak Street, Dallas 75221.

May 8—**Pediatrics Lecture.** Sponsored by Los Angeles Pediatrics Society in Los Angeles. Thursday. Contact: Mrs. Eve Black, Executive Secretary, P.O. Box 2022, Inglewood 90305.

May 8-10—**Advances in Pediatrics.** UCSF. Thursday-Saturday.

May 8-10—**Association of University Radiologists.** UC Medical Center, San Francisco. Thursday-Saturday. Contact: Harry Z. Mellins, M.D., Department of Radiology, State University of New York, Brooklyn 10021.

May 9-10—**REDWOOD REGIONAL CONFERENCE.** Sponsored by CMA, UCLA and North Coast Counties Medical Societies at Konocti Harbor Inn, Clear Lake. Friday-Saturday. 14 hours. $20. Contact: CMA.

May 9-10—**Effective Medical Writing.** UCLA School of Medicine Extension Division in cooperation with the Southern California Chapter of the American Medical Writers Association. Ambassador Hotel, Los Angeles. Friday-Saturday. Contact: UCLA.

May 9-11—**Annual Meeting, San Francisco Neurosurgical Society.** Del Monte Lodge, Pebble Beach. Friday-Sunday. Contact: Burton L. Wise, M.D., Room U-120, UC Medical Center, San Francisco 94122. (415) 666-1677.

May 10-11—**Love, Sex, Marriage.** UCSF at Mendocino State Hospital, Talmage. Saturday-Sunday.

May 12-15—**American Urological Association.** Hilton Hotel, San Francisco. Monday-Thursday. Contact: William P. Didusch, Executive Secretary, 1120 North Charles Street, Baltimore 20201.

May 12-17—**American Association on Mental Deficiency.** Sheraton-Palace Hotel, San Francisco. Monday-Saturday. Contact: John J. Noone, Ed.D., Executive Secretary, 5201 Connecticut Avenue, N.W., Washington, D.C. 20015.

May 15-17—**Ear, Nose, Throat.** UCSF. Thursday-Saturday.

May 16 — **Scientific Session, Annual Physician Symposium.** California Heart Association and Council on Clinical Cardiology in cooperation with the American Heart Association. Jack Tar Hotel, San Francisco. Friday.

May 17—**Application of Casts, Splints and Bandages.** UCLA. Saturday.

May 17—**Annual Seminar and Barbecue.** General Hospital of Ventura County. Saturday. Contact: Gerald K. Ridge, M.D., 3291 Loma Vista Road, Ventura.

May 21—**East Meets West.** Agnews State Hospital, San Jose. Wednesday. Contact: J. Elizabeth Jeffress, M.D., Chief of Professional Education, Agnews State Hospital, San Jose 95114.

May 23—**What's New in Medicine (UC Alumni Day).** San Francisco. Friday. Contact: UCSF.

May 23-24—**14th Annual OB/GYN Symposium.** Southern California Permanente Medical Group. Beverly Hilton Hotel, Los Angeles. Friday-Saturday. Contact:

Mrs. Shirley Gach, 4900 Sunset Boulevard, Room 3007, Los Angeles 90027.

May 23-25—**Arthritis Program.** UCSF. Friday-Sunday.

May 23-25—**Frontiers in Medicine.** UCSF and Humboldt-Del Norte Medical Society in Eureka. Friday-Sunday. Contact: UCSF.

May 23-25 — **Cardiac Roentgenology.** UCLA at the Century Plaza Hotel. Friday-Sunday.

May 23-25—**Computers in Medicine.** UCSF. Friday-Sunday.

May 24-25—**Psychiatry Program.** UCSF in Sacramento. Saturday-Sunday.

May 24-25—**A Conference in Psychiatry.** UCSF at De Witt State Hospital, Auburn. Saturday-Sunday.

May 24-25 — **Treatment of Anxiety and Depression.** UCLA. Saturday-Sunday.

JUNE

June 5-7—**Highlights of Ophthalmology.** PMC. Thursday-Saturday.

June 5-7—**Sacramento Valley Counties Regional Postgraduate Institute.** California Medical Association in cooperation with UCSF and Sacramento Valley Counties Medical Societies. Sahara Tahoe Hotel, Lake Tahoe. Thursday-Saturday. $20. Contact: CMA.

June 6-7—**Vectorcardiography.** UCSF. Friday-Saturday.

June 7 — **Office Management.** UCLA at St. Joseph's Hospital, Burbank. Saturday.

June 10-14 — **Electrophoresis Workshop.** UCSF at Children's Hospital. Tuesday-Saturday.

June 18—**My Third Year of Residency Training with Professor Carstairs.** Agnews State Hospital, San Jose. Wednesday. Contact: J. Elizabeth Jeffress, M.D., Director of Professional Education, Agnews State Hospital, San Jose 95114.

June 19-21—**American Medical Women's Association.** Alta Mira Hotel, Sausalito. Thursday-Saturday. Contact: Mrs. Gertrude F. Conroy, 1740 Broadway, New York 10019.

June 20-21—**Postgraduate Seminar: Pediatrics.** Children's Hospital of Orange County, Orange. Friday-Saturday. $30. Contact: Merl J. Carson, M.D., Medical Director, Children's Hospital of Orange County, 1109 West La Veta Avenue, Orange. (714) 538-8831.

June 23-25—**Postgraduate Course in Ophthalmology.** Stanford University. Monday-Wednesday. $100. Contact: Division of Ophthalmology, Stanford University School of Medicine, Stanford 94305.

June 28-29—**Nasal Reconstruction.** UCLA. Saturday-Sunday.

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NEWS & NOTES

NATIONAL • STATE • COUNTY

LOS ANGELES

A seminar on **New Frontiers in Aging** is to be held 10 May 1969 under the sponsorship of the medical staff of Valley Presbyterian Hospital in Van Nuys. Guest speakers are Dr. Peter Forsham, University of California San Francisco Medical Center, Dr. Michael E. DeBakey, Baylor University College of Medicine, and Dr. Charles Dotter, University of Oregon Medical School.

ORANGE

The fourth annual **postgraduate seminar**, presented by Childrens Hospital of Orange County, Orange, will be held on June 20 and 21, 1969, at the hospital facilities. Guest speakers will include Dr. Richmond S. Paine, Dr. Vincent A. Fulginiti, Dr. Samuel P. Bessman, Dr. Carl Cotman, Dr. Frank Taylor, and others. The program is designed to present the latest information regarding **immunology, infectious disease, and pediatric neurology.** For information write: Merl J. Carson, M.D., Medical Director, Childrens Hospital of Orange County, 1109 W. La Veta, Orange 92668.

SAN FRANCISCO

A U.S. Public Health Service grant for approximately two and a half million dollars over a five-year period to establish a **Clinical Cancer Research Center** at the University of California San Francisco Medical Center, has been announced by Dr. David A. Wood, director of the Cancer Research Institute on the San Francisco campus. Dr. Martin J. Cline, associate professor of medicine and associate director of the institute, will be program director for the center, which will emphasize close coordination between basic science research and clinical application.

* * *

A postgraduate course on **Recent Advances in Pediatrics** will be held May 8 to 10 at the University of California San Francisco Medical Center. Advances in neonatology, cardiopulmonary disease, renal and electrolyte disorders, endocrine aberrations, gastrointestinal disorders, human chromosomal abnormalities and infectious diseases will be discussed.

The course is presented by the Department of Pediatrics and by Continuing Education in Health Sciences. Further information may be obtained from Seymour M. Farber, M.D., UC Medical Center, 401 Parnassus Avenue, San Francisco 94122.

* * *

A postgraduate conference on **Highlights of Modern Ophthalmology** will be held June 5 to 7 at Presbyterian Hospital of Pacific Medical Center, San Francisco. The conference will feature material on cryosurgery, fluorescein angiography, glaucoma, cataract surgery, treatment of diabetic retinopathy, and new operations for retinal detachment. The guest speaker will be Dr. Charles Kelman who will present his material on the **ultrasonic techniques for cataract extraction.** Further information may be obtained from the Department of Continuing Education, Pacific Medical Center, San Francisco 94115.

SANTA CLARA

Two gifts to the **Stanford University School of Medicine** totalling $275,000 were announced recently by Dr. Robert J. Glaser, vice-president for medical affairs and dean of the medical school.

A gift of $125,000 to expand the school's **cancer treatment facilities** was received from the Louis B. Mayer Foundation, bringing to $870,000 the total raised for expansion of Stanford's radiation treatment facilities.

The other award, a three-year grant totalling $150,000, was made by the Donald E. Baxter Foundation of Los Angeles. The foundation stipulated that 20 percent of the funds be used for the **medical student aid program** at Stanford with the balance being available for general medical research.

* * *

The Santa Clara County Radiological Society has announced its new officers for the coming year: Drs. Charles L. Rennell, president; D. Brendan O'Donnell, president-elect; John J. Berg, secretary; and Ivan S. Fucilla, treasurer.

YOLO

Dr. Reed M. Nesbit of Davis has been named chairman of the Board of Commissioners of the Joint Commission on Accreditation of Hospitals. The Joint Commission is the agency principally charged with the review and evaluation of the quality of hospital service in the United States. Its member organizations are the American Hospital Association, the American Medical Association, the American College of Physicians, and the American College of Surgeons. Dr. Nesbit represents the American College of Surgeons.

GENERAL

Two hundred volunteer physicians are urgently needed to maintain the **Volunteer Physicians for Viet Nam** program at its current level throughout 1969, according to recent announcement from Dr. Charles H. Moseley, director of the program. Those who sign up for the program are scheduled for 60-day tours. The greatest need, Dr. Moseley said, is for general practitioners, internists, pediatricians, preventive medicine specialists, general surgeons, orthopedic surgeons and ophthalmologists. A limited number of volunteers from other specialty groups (anesthesiology, dermatology, obstetrics-gynecology, otorhinolaryngology, clinical pathology, physical medicine, radiology and urology) can be effectively utilized for selected assignments at specific sites, he said. Since inception of the program in 1965, far **more of the volunteer physicians have come from California** than from any other state—83, against 47 for second place New York.

HOW TO GET PAID FOR TREATING MILITARY PATIENTS

Payment to civilian sources for emergency professional **services rendered to military personnel** who are on active duty (as contrasted to retired, or inactive members of the National Guard or Reserve) is the responsibility of the Surgeon of the geographical area in which such services are provided. Collection cannot be made from the Office for the Civilian Health and Medical Program for the Uniformed Services (OCHAMPUS), Denver, Colo., or its fiscal agents, who are responsible only for the payment of medical care rendered to authorized dependents and retired military personnel.

When a patient is identified as an Army member, on active duty, notification should be made immediately by telephone to the appropriate Army headquarters (in California: Commanding General, Sixth U.S. Army, Attention, Surgeon, Presidio of San Francisco, Calif., 94129. Area Code 415—Weekdays: 561-3945 or 4287; nights, weekends and holidays: 561-2497 or 2780). A report should be given of where the individual is and the nature of the treatment required. The cost of the telephone call will be reimbursed with the other charges.

The Army headquarters will advise the caller about the administrative management of the patient, and how to submit the bills for service.

FLEX THE HEAD IN INTUBATING THE NEWBORN

"Remember in intubating the newborn: Do not extend the head. If you extend the head, the larynx becomes higher in the neck; it becomes even more anterior; and intubation is extremely difficult to do. If you flex the head, it's a lot easier."

—Penelope Cave, M.D., Palo Alto
Extracted from *Audio-Digest Anesthesiology*, Vol. 10, No. 21, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

BOOK REVIEWS

California Medicine does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

PAEDIATRIC CARDIOLOGY—Edited by Hamish Watson, T.D., M.D. (Ed.), F.R.C.P. (Ed.), M.R.C.P. (Lond.), consultant physician and cardiologist, Dundee Group of Teaching Hospitals, and senior lecturer in clinical cardiology and paediatric cardiology, University of Dundee. The C. V. Mosby Co., 3207 Washington Boulevard, St. Louis, Mo. (63103), 1968. 996 pages, $36.50.

During the last three years, a number of encyclopedias of pediatric cardiology have been published. Dr. Watson's *Paediatric Cardiology* is the latest of the multiple contributor volumes. The general chapter arrangement of this book is similar to others. A few general chapters precede discussion of specific lesions. The embryology chapter is well illustrated and Rudolph's chapters concerning fetal and pulmonary circulation are amongst the highlights of the book. The electrocardiography chapter is well written and contains many useful charts. This is the only pediatric cardiology textbook to devote a chapter to tropical diseases of the heart. It is surprising that so little attention is accorded to vectorcardiography in a modern textbook. The cardiac catheterization chapter is particularly weak and the radiology chapter neglected discussion of quantitative chamber volumes, an important feature of modern cardiology. The chapters concerning specific lesions are generally acceptable, but lack detailed natural history information. Although Cooley concluded the book with a short chapter concerning operative features of congenital cardiac disease, this would seem inadequate for a subspecialty so closely aligned to cardiac surgery. A cardiac pharmacology chapter would have been a most useful addition.

In final analysis, *Paediatric Cardiology* has some serious deletions, and probably would not be as suitable as other books covering the same area if one were restricted to a single volume dealing with pediatric cardiology. On the other hand, there can be no doubt that it can serve as a reference, particularly if complemented with one or more of the other recent texts.

Stanley J. Goldberg, M.D.

* * *

THE FEAR OF WOMEN — Wolfgan Lederer, M.D. Grune and Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1968. 360 pages, $12.50.

It is unfortunate that a book of such exquisite brilliance must bear a limited and misleading title. I am afraid that an appeal on the jacket to paperback curiosity will obscure the intent of the author and drive away the very souls who would find appreciation in the heart of the book, which is an epic for any shelf.

More than the title would imply this is a history of the depiction of the female concept. Perhaps one might think of it as "Woman, The Distorted Legend," or "The Feminine Image in Art and Fable."

The colorful and appealing background of Dr. Lederer is displayed on the paper cover by the Park Avenue publisher to lure the browser, but modestly omitted in the book itself, where it belongs. Born in Vienna, this scholar and soldier is Clinical Assistant Professor of Psychiatry at the University of California School of Medicine in San Francisco.

The introduction is a nauseating hurdle to get over as quickly as possible. In it Dr. Lederer, to make his point, beats the psychiatric tom-tom by conjuring up a dread of women supposed secretively to pervade the masculine world and lead to all manner of perversions, neuroses, and strange behavior, unto the ultimate destruction of the universe. As a gynecologist I feel somewhat deprived that I cannot revel with him in this moon thing about fellow humans.

The fruit of the endeavor, if the author will pardon the expression, is strewn throughout the main text. He begins with Freudian and post-Freudian voodooism to support the Oedipus cults and to mystify the external genitalia of woman, such as they are.

Freud, you will recall, came into the tabloids and drawing rooms in the 20's with sex as the center of the universe. After a brief play he was considered a Goliath slain by a grain of salt, but in the 60's he is up again for capital gains.

As a gem of Merlinism he is quoted as stating that Medusa's head represents the vulva. And to gild that one, he goes on to make penises of the snake-like hairs of the severed (castrated yet) caput. In my dotage I'm beginning to think that Sigmund was a little meshugge.

And so it follows that the old penis-envy presumption is flaunted again, for all it's worth and more.

A chapter on the Fat Venus is enlightening and interesting, especially in these high caloric times, and displays a worship of female figures in stone and other materials over the thousands of years that have gone. Illustrations are offered showing engaging variations in the generous proportions. The historical record is fascinating, and the restraint shown in interpretation is reassuring.

Maternity and breast feeding are idolized in primitive symbolism. The theme is archaic and boring. A great deal is made of ochre as the "oldest lasting pigment approaching red" and its presence in art. As you may have guessed, it is supposed to signify menstrual blood, and we launch into the same old litany we read in high school, steaming with academic spiritualistic vocabulary. You could smell "tabu" and "unclean" coming up on each succeeding page.

It may be that this book is written in part from the couch. In his chapter "Frau Welt, Or The Perfume of Decay," the text reads:

> "I can still vividly recall something else about old women—not their appearance, but their smell. Perhaps it is something about post-menopausal chemistry; more likely it had to do with certain physical neglect once physical charms were past. At any rate, what with modern hygiene and modern perfume, I

have not noticed it lately; when I still noticed it—for the last time, I think, during my medical internship—I could not get away from it fast enough."

Further notes are made describing the smells of menstruum and of vaginal infections, with appropriate folklore. All chivalry aside, I fail to recognize these fine sommelier distinctions in vintage. Rather, I should pronounce the post-menopausal patient remarkably devoid of intrinsic scent, and find pleasant the hint of the sachet, or the lilac, as a touch of nostalgia near the cave of Nevermore, whence the evil goddess Monilia has long fled in search of flesh more redolent with sugary syrup of glycogen, and of progesterone.

But please forgive the reverie. To read this book does encourage a trance-like state, and in spite of my analysis, it holds together as a compelling and enchanting history of pelvic witchcraft.

A chapter on vaginal teeth, and sundry relics, gives us a serious discussion of another superstition which has formed the basis for occasional barracks room ballads.

Gynecotoxicology is exhibited as well as more direct violence, in the manner of Scylla, Borgia, and poor Lizzie Borden.

Mom-ism is portrayed in a less humorous manner than Huxley's bittersweet warning, but with individual applications rather than social overtone. It is one of Lederer's better chapters beneath the symbolism and recurrent homage to the great god, Freud. Infanticide and mutilation, on to paedophagia, enjoy a hoary chapter designed to coagulate your corpuscles and make you look askance at your next baby-sitter.

Pandora's box comes at you like a telegraphed punch, interpretations galore, not to mention a recently popularized first name. Duck that chapter. For sheer delight go on to the one entitled "Fire Is Not Sated With Word," in which the hell-hath-no-fury theme is elaborated in a most beguiling style.

Feminine "logic," household regency, woman as a vessel, a goddess, a monster, a prophetess—all are treated in historical and legendary fabrics, and then brought up into the present with modern applications—for future reference.

Make no mistake, the deeper into this book we travel the more enchanting it becomes. Once having learned to dodge the psychiatry, and all that, it is apparent that this is a volume which will add another facet to the personality of the physician or the lay person, male or female, old or young. James Thurber would have relished this work, and I'll wager Dr. Lederer relishes Thurber.

If a former tank-destroyer company commander, wounded in the service of this slowly fading nation, can produce a work of such magnitude, I wish he'd come out of his psychoanalytic orbit and back to his fellows. We need a few guys like this around today. And buy the book—it's a gem!

GORDON BURR MILLER, M.D.

* * *

CURRENT DIAGNOSIS—2 (2nd Edition)—Edited by Howard F. Conn, M.D., and Rex B. Conn, Jr., M.D. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1968. 990 pages, $21.75.

No doubt this book will be selected by many busy practitioners to complement Conn's *Current Therapy* as a handy desk reference, but all in all, it has little to recommend it over the *Merck Manual* at one-half the price and weight. It is elementary and superficial in many sections; unbalanced, and fails to deliver the "impressive number of diagnostic increments in our capabilities" promised in the preface. A more lengthy treatment is given to the definition, incidence, etiology, pathology and complications of diseases in many sections than to the details of diagnosis by clinical, laboratory and x-ray methods. The decision to include a separate section with its individual author to aid the reader in the diagnosis of pimples reflects the judgment exercised by the editors to be all-inclusive, rather than incisive and illuminating. The selection of two fellows-in-training and four resident physician authors for this text hardly supports the editors' claim of "leading medical authorities in the United States and abroad" as contributors to this second edition.

Nine pages are devoted to the diagnosis of aerophagia and a single page to multiple sclerosis. The brain scan is described as a valuable method to distinguish a malignancy from infarction, but no details are given in either section on how this distinction is made. We are offered the serum uric acid determination as the best test for gout, then told the diagnosis should be based on clinical findings if the uric acid is normal. Exercise stress testing receives scant attention in the diagnosis of ischemic heart disease, and less than ten lines are devoted to coronary arteriography.

There are some excellent sections, of course. The differential diagnosis of systemic hypertension is presented by Dr. Ray Gifford in a lucid comprehensive manner. The congenital heart defects are very well described. Jesse Steinfeld's description of the diagnosis of leukemias is outstanding. These highlights, however, are not sufficiently abundant to offset the many prosaic descriptions of routine diagnostic tests well known to most practicing physicians. This book therefore cannot be recommended as a significant addition to the standard textbooks of medicine now available.

JOHN A. UDALL, M.D.

* * *

PRACTICAL PSYCHIATRY FOR THE INTERNIST — Douglas Goldman, M.D., Chairman, Department of Psychiatry, Good Samaritan Hospital, Cincinnati, Assistant Clinical Professor, Department of Psychiatry, University of Cincinnati College of Medicine, Cincinnati; and George A. Ulett, M.D., Ph.D., Director, Missouri Division of Mental Diseases, Professor of Psychiatry and Chairman, Department of Psychiatry, University of Missouri School of Medicine, Missouri Institute of Psychiatry, St. Louis. The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis, Mo. (63103), 1968. 168 pages, $9.85.

Perhaps no contribution to medical literature would be more valuable or more timely than a work that would succinctly and lucidly epitomize and convey the facts and theory of current psychiatric practice to the other specialties of medicine.

It would be a pleasure to say that these aims had been met in this present volume with its engaging and exciting title. But, alas, this, in the opinion of this reviewer, is unhappily not the case. The faults and deficiencies of this book are many. The general impression it gives is one of superficiality and incompleteness, and even in those matters which are more fully discussed there is a spotty and uneven focus. The dynamics and genesis of human behavior are mentioned almost not at all and when they are presented the description manages to be both simplistic and turgid. Almost no attempt is made to even cursorily cover the categories, varieties and types of psychosomatic disorders, and also there is scant representation of the now quite considerable body of knowledge about short-term psychotherapeutic techniques that can be successfully employed by non-psychiatric physicians. The book has one excellent section; namely, the chapter on psychopharmacology, in which the subject is both completely and clearly presented. The rest of the book, however, is largely disappointing.

CHARLES W. WAHL, M.D.

PROGRESS IN GASTROENTEROLOGY—Volume 1—Edited by George B. Jerzy Glass, M.D., New York Medical College, New York, N.Y. Grune and Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1968. 520 pages, $29.50.

This first of two expected volumes of *Progress in Gastroenterology*, edited by Dr. Glass, has special emphasis on the stomach and the small intestine. It contains 20 papers by 32 authors and has more than 1800 references.

The x-rays, electron micrographs, pathological specimens and diagrams are clearly reproducted on fine quality paper. The chapters in the book give information that is current and accurate.

This book is recommended for anyone interested in the field of gastroenterology, including clinicians, researchers and physicians in training. The bibliographies accompanying each paper are excellent. The editor and its authors are to be congratulated for producing an outstanding new book in the field of gastroenterology.

DWIGHT L. WILBUR, III, M.D.

* * *

CLINICAL METHODS IN UVEITIS — THE FOURTH SLOAN SYMPOSIUM ON UVEITIS—Edited by Samuel B. Aronson, M.D., Assistant Professor of Ophthalmology in Residence; Charles N. Gamble, M.D., Associate Clinical Professor of Pathology; Ernest K. Goodner, M.D., Assistant Clinical Professor of Ophthalmology, Research Ophthalmologist, Francis I. Proctor Foundation; and G. Richard O'Connor, M.D., Assistant Clinical Professor of Ophthalmology, Associate Director, Francis I. Proctor Foundation; all of the University of California, San Francisco, Calif. The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis, Mo. (63103), 1968. 248 pages, with 66 illustrations, $18.25.

Contributors to this symposium numbered 23 persons, mostly ophthalmologists, but also including members of departments of Medicine, Pathology, Biometry and several research institutes. Additional participants numbered 25 and were drawn from institutions throughout the United States, Canada, England and Switzerland.

The clinical aspects of uveitis are thoroughly studied and discussed in a series of prepared papers grouped under three main headings and a number of sub-headings, with open discussion and criticism encouraged at the conclusion of each subheading.

The subjects discussed are: epidemiology and biostatics, historical aspects, and techniques employed in uveitis surveys, the role of the internist and allergist in evaluation and treatment of uveitis, anatomic pathology and experimental biology in uveitis and the place of the diagnostic laboratory in evaluation of this disease. Finally, the current problems in uveitis surveys are discussed at length and suggestions made for future studies.

As is often the case in the publication of such symposia, the format is somewhat disconnected and it is sometimes difficult to get at the meat of the discussion. This is due, no doubt, to the mass of material which must be digested by the editors and correlated into a concise whole. Considering the difficult nature of the subject and the controversy which has raged around some of the material, the editors are to be congratulated on their compilation of the data and arguments presented to them.

Some of the prepared papers in this symposium are excellent and considerable new material is presented. Some are largely review of previously published material. It would appear obvious that most of the participants in this symposium went home more knowledgeable than when they came. A study of their edited contributions should be of value to all ophthalmologists and to those members of other disciplines who may from time to time encounter this difficult and disabling clinical entity.

DAVID O. HARRINGTON, M.D.

* * *

DIARY OF A HEART PATIENT—Yehuda Kesten. McGraw-Hill Book Company, 330 West 42nd Street, New York, N. Y. (10036), 1968. 272 pages, $7.95.

The author, presently education-editor and science-correspondent of an Israeli newspaper, reports he is the first victim of Marfan's syndrome to be diagnosed in his country. The aneurysm of his thoracic aorta was resected and, a year later, his aortic valve was replaced by Dr. DeBakey. The two open-heart operations are the subject of the book, written a year after the second.

Unhappily for the medical reader, the book is grossly under-edited. Although the author-patient consulted editorially with "a most successful young heart surgeon," the book abounds with errors, some stupid, some sophisticated. On page 11, pus is twice misspelled puss. The musculature is called the musculatory system. Vaccination against bubonic plague is said to be required to enter this country (p. 39). That Marfan in his original paper did not include dislocated lenses in the syndrome should have been mentioned. Redundancies ("Naval Officers School of the Navy") are frequent. The last of four features of the Marfan-syndrome skull is referred to as "the latter." Misspellings are many: the Bovie unit is once Bovee and then Bovi; ostium is osteum; Diuril is Diuryl. Metaphors are often inappropriate: "the ends standing up diagonally like the ears of a thoroughbred hound" (p. 91). Since the author is a journalist and the publisher is first-rate, these annoyances, so easily eliminated by editing, become irritations.

That his sweetheart's visit to him in the hospital helped him is understandable. But when, after the liaison was severed between operations, he picked up a girl in a New York subway, the reader should be spared the tasteless details.

Since Marfan's syndrome is rare, the book loses much of its value for families who must accept open-heart surgery for one of their kin. Nevertheless, the description of the patient's ordeal is well written, without egotism or heroics, and may serve to encourage hope in future candidates.

Dr. DeBakey, the co-hero of the book, is given a genius-sized halo as well as a number of arrows. Mrs. DeBakey fares better; as her husband's alter ego, she comes in for grace and devotion. The Methodist Hospital and its staff are deservedly applauded.

On page 14, the author approaches the value of the psychiatrist for the patient with physical disease that forces life-threatening treatment. Regrettably, he does not amplify this concept.

All in all, the book is not recommended. The classic ordeal of open-heart surgery remains to be written.

EDWARD SHAPIRO, M.D.

California
Medicine

Cerebral Syndromes of Diabetes Mellitus

HENRY S. SHAVELLE, M.D., *Long Beach*

■ *Three labile diabetic patients had recurring episodes of altered sensorium. Each had severe cerebrovascular disease with superimposed metabolic derangements, including ketoacidosis, hyperglycemia without ketosis, mild uremia, and possibly cerebral edema. Two of the patients were examined postmortem. Severe leptomeningeal scarring, basal ganglial calcification and destruction of small intracerebral vessels without evidence of large vessel atherosclerosis were found unexpectedly in one patient, a rare occurrence in this country although recently reported from Europe. The other patient had large vessel atherosclerosis only.*

The clinical expression of the vascular disease was modified by concurrent abnormalities and reflected the sum total of the complexities which coexisted. The pathophysiology of the unconscious state necessarily depends on the inciting factors. Ketoacidotic coma is associated with depressed cerebral oxygen consumption. Spinal fluid pH is usually maintained during ketosis but is sometimes lowered inadvertently during bicarbonate therapy, with resultant coma. Other variables influencing the clinical expression, with or without ketosis, would include, among others, blood viscosity alterations, rapid decrements in blood sugar, and existing degrees of lactic acidosis.

The increasing life-span of the juvenile diabetics, favorably influenced by improved management and recently by hemodialysis, may uncover vascular complications heretofore rarely seen and create additional diagnostic and therapeutic enigmas.

IMPAIRED CONSCIOUSNESS in diabetic patients has many diverse causes (Table 1). Metabolic and non-metabolic disturbances associated with diabetes continue to be added to this growing list as knowledge and therapy of the diabetic state improve. A specific structural diabetic encephalopathy also has been mentioned, mostly in the European literature.[1] Because of concurrent hypertension, uremia, or far-advanced atherosclerotic cerebrovascular disease occurring in severely ill diabetic patients, there has been a natural reluctance on the part of clinicians to consider any encephalopathy as specific only for diabetes.

From the Department of Medicine, Harbor General Hospital, Torrance, and UCLA School of Medicine, Los Angeles.

Submitted, revised, 28 January 1969.

Reprint requests to: 3736 Atlantic Avenue, Long Beach 90807.

TABLE 1.—*Causes of Impaired Consciousness Peculiar to Diabetic Subjects*

1. *Diabetic Ketoacidosis.*
2. *Hypoglycemia,* due to oral hypoglycemic agents, insulin therapy, or as an early manifestation of subsequent diabetes.
3. *Hyperosmolar Hyperglycemic Non-Ketotic Coma.*
4. *Lactic acidosis,* subsequent to ketoacidosis or associated with phenformin therapy.
5. *Cerebrovascular disease* (thrombosis, ischemia, less frequently hemorrhage), due to accelerated atherosclerosis, or occurring in the course of diastolic hypertension secondary to diabetic nephropathy.
6. *Infection,* especially phycomycoses.
7. *Uremia,* due to diabetic nephropathy.
8. *Cerebral edema,* as a complication of ketoacidosis.

Within a period of two-and-a-half years we have noticed, among our large numbers of diabetic inpatients and out-patients, several patients with varying neurological states, ranging from confusion and lethargy to profound coma. The following report illustrates the repeated neurological abnormalities and clinical courses of three such patients having severe vascular disease with superimposed metabolic derangements. It is our purpose, first, to review the problems and pathophysiology of cerebral dysfunction in labile diabetic patients and, second, to suggest that a particular vascular encephalopathy is more prevalent in patients with long-standing diabetes although not specific.

Reports of Three Cases

Case 1. The patient was a 22-year-old Caucasian woman who had been diabetic since age 5. Control was never satisfactory on long-acting insulin, necessitating use of 20 units of regular insulin before breakfast, lunch and dinner. She had severe retinopathy with poor vision and diabetic glomerulosclerosis; and recently the nephrotic syndrome had developed.

On 10 February 1965, right-sided numbness of the face, arm and leg developed, and the patient became incoherent. There had been no previous episodes of speech difficulties, paralysis or seizures. Blood pressure was 195/85 mm of mercury, the pulse 112 and regular, respirations 12 per minute and temperature 100.5° F. The patient was lethargic and disoriented, with slurred speech and vomiting. General examination was unremarkable although the mucous membranes were dry and skin turgor was slightly diminished. The pupils reacted to light but vision could not be tested and the fundi were not seen. Cranial nerves III-XII were intact. She moved all extremities well and deep tendon reflexes were active and symmetrical with the exception of the absence of ankle jerks. Toe signs were equivocally abnormal. Laboratory data included: urinalysis, trace of sugar and slight acetone; blood glucose, 87 mg per 100 ml; bicarbonate, 14 mEq per liter; chloride, 103 mEq per liter; blood urea nitrogen, 30 mg per 100 ml; leukocytes, 12,000 per cu mm.

There was no response to rapid intravenous administration of 50 ml of 50 percent glucose solution. The next day the patient was afebrile but nuchal rigidity and a right lower facial weakness were noted. Lumbar puncture revealed an opening pressure of 140 mm (water) and closing pressure of 110 mm with clear fluid having protein content of 14 mg and sugar 280 mg per 100 ml (simultaneous blood sugar was 300 mg per 100 ml), and 25 cells per cu mm, 21 of which were polymorphonuclear. Subsequent bacteria and fungal cultures were negative. On 12 February, the patient had a generalized tonic-clonic seizure with the eyes at first deviated to the right and later to the left. Lumbar puncture was repeated and the findings were essentially unchanged. A brain abscess was suspected although the patient remained afebrile and blood cultures were negative. The next day she made some response to commands, and limitation of right lateral conjugate gaze was noted. On 14 February she responded slowly but appropriately, and sensory examination was intact to pain, position, vibration and stereognosis. On 16 February horizontal and vertical nystagmus was noted along with persistent right lateral conjugate gaze weakness. A thrombotic or ischemic lesion was now suspected. An electroencephalogram was essentially normal (symmetrical alpha activity, no alteration with hyperventilation, and no focal or paroxysmal abnormalities). Skull x-ray films were normal. Throughout the stay in hospital, blood pressure varied from 150/90 to 180/100 mm of mercury and blood glucose varied from 60 to 1,200 mg per 100 ml. Despite these wide fluctuations there was steady neurologic improvement, and she was discharged 31 days after admission with no residual difficulty other than poor visual acuity.

Subsequent examinations demonstrated no neurological deficits aside from a mild peripheral neuropathy and progressive loss of vision.

On 17 June 1965 she was readmitted, confused and agitated, and gradually she lapsed into a comatose state. Blood pressure was 210/110; other vital signs were stable. Pupils were nonreactive. Cranial nerves were otherwise intact. She moved all extremities well, deep tendon reflexes were active, and toe signs were flexor. A tonic-clonic seizure was observed. Blood sugar was 444 mg per 100 ml, bicarbonate was 15 mEq and sodium 130 mEq per liter, serum acetone a trace at no dilution, blood urea nitrogen 50 mg per 100 ml, and urinalysis reactions strong for sugar and negative for acetone. Lumbar puncture revealed an opening pressure of 260 mm of water, closing pressure 140 mm, clear fluid with no cells, and protein 44 mg per 100 ml. The patient remained comatose, responding only to pain, until 20 June when she gradually improved to her previous state of health.

During the months of July and August, her insulin requirements decreased; recurrent hypoglycemic reactions were common.

On 6 September 1965 she presented with convulsions, was semi-comatose and had a blood pressure ranging from 180/80 to 240/120 mm of mercury. Results of neurological examination were as before. Blood sugar was 1210 mg per 100 ml, serum acetone a trace at no dilution, blood urea nitrogen 85 mg per 100 ml, sodium 127 mEq, chloride 92 mEq and bicarbonate 15 mEq per liter. She had a cardiac arrest the next day and was resuscitated but thereafter remained in a profound, flaccid, comatose state and died nine days later. Postmortem examination revealed generalized arteriosclerosis with severe atheromatous involvement of the circle of Willis. The brain showed no evidence of herniation or flattening of convolutions, and no areas of softening or hemorrhage were seen. Microscopic study was unremarkable and the smaller arterioles of the cerebrum showed nonspecific medial thickening only.

Comment

The patient's clinical course during the first two hospital admissions initially presented a diagnostic dilemma although it later became evident that she was having episodes of focal cerebrovascular dysfunction, probably associated with other functional alterations. Her lesion was obviously in a vascular distribution and the differential diagnosis might have included a "small stroke," small vessel disease, recurrent cerebral emboli, and hypercoagulability.

Her last acute episode was due to hyperosmolality associated with nonketotic hyperglycemia, not usually seen in juvenile diabetics.[2,3]

Case 2. The patient was a 41-year-old Caucasian woman who had had diabetes since age 11 and was taking 45 units of Lente insulin daily with suboptimal control. She had had numerous admissions to this hospital in the past and was severely afflicted with most of the complications of longstanding diabetes, including retinopathy, peripheral neuropathy, nodular glomerulosclerosis and gastroparesis diabeticorum.

On 12 August 1966, while being seen in the clinic, she began to vomit and was unable to communicate. Blood sugar was 72 mg per 100 ml. There was no response to 25 ml of 50 percent glucose solution by rapid intravenous administration. On admission to the hospital the patient was crying, uncooperative and thrashing about. Blood pressure ranged about 190/120 mm of mercury, the temperature was 100.4°F, pulse 104 and respirations 28. General examination was unremarkable. Funduscopic examination revealed hemorrhages and exudates with clear disc margins. Cranial nerves were all intact. Deep tendon reflexes were active in the upper extremities, diminished in the knees, absent in the ankles, with no pathological toe signs. Blood sugar was 185 mg per 100 ml, blood urea nitrogen 16 mg per 100 ml, and electrolytes were within normal limits. The admission diagnosis was hysterical reaction. The next day the patient was alert and feeding herself but complained of headaches. Blood sugar at that time was 59 mg per 100 ml. She was alert on 15 August and was placed on a sliding insulin scale according to urine glucose spillage. She received no insulin from the morning of 15 August to 16 August, at which time she became agitated and threatened the nurses. Blood sugar at 12 noon was 810 mg per 100 ml, bicarbonate 14 mEq per liter, and serum acetone 2+ at 1:2 dilution.

Three hours later, the patient again complained of severe right-sided headaches and then became non-responsive. Bilateral papilledema was noted, as well as a left facial droop and a left flaccid hemiparesis. The neck was rigid and there was a positive Brudzinski's sign. Carotid pulsations were full. Temperature was 104°F. Lumbar puncture revealed clear fluid, an opening pressure of 360 mm of water, sugar 300 mg per 100 ml, and no cells.

Treatment consisted of insulin and fluids only. The differential diagnosis at this time included the strong possibility of a right hemispheric mass lesion

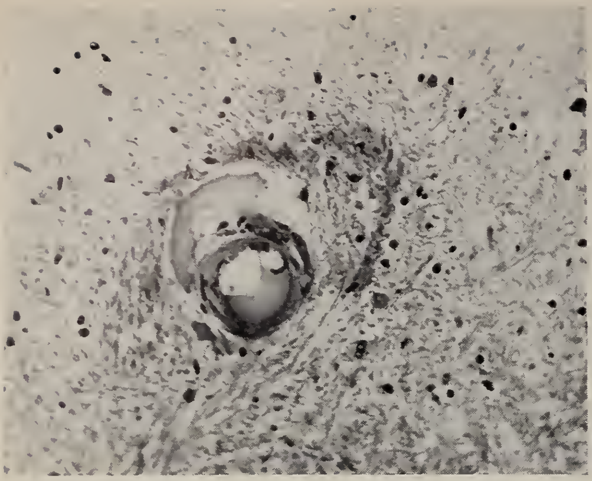

Figure 1.—Photomicrograph of cerebral cortex from patient in Case 2, showing intimal proliferative and occlusive changes in a small arteriole. (Hematoxylin and eosin, x 200.)

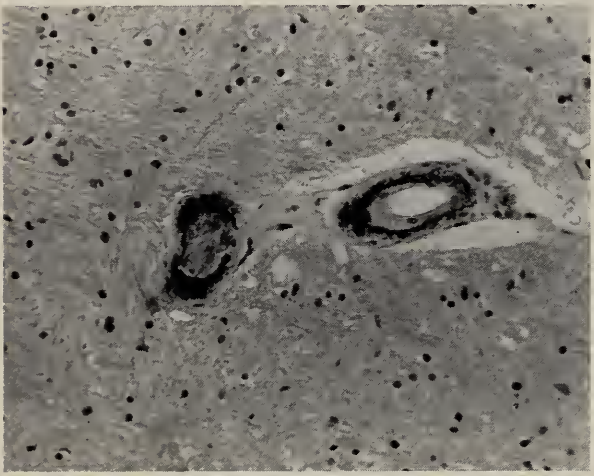

Figure 2.—Photomicrograph of cerebral cortex from patient in Case 2, showing pronounced siderocalcinosis in a medium-sized arteriole. (Hematoxylin and eosin, x 100.)

due to either an abscess, a subdural hematoma, an intracerebral hematoma, or a septic embolus from bacterial endocarditis.

A right carotid angiogram was within normal limits. Numerous blood and spinal fluid cultures remained sterile. That evening, the serum bicarbonate was 23 mEq per liter, blood pressure was 160/100 mm and the patient was incoherent. She became afebrile the next day and began to have purposeful movements of her left arm shortly thereafter but remained confused.

Electroencephalography on 19 August showed low voltage background with infrequent 8 to 9 cycles per second posterior alpha activity, best seen on the left, with a moderate amount of random fronto-temporal theta activity. In general the

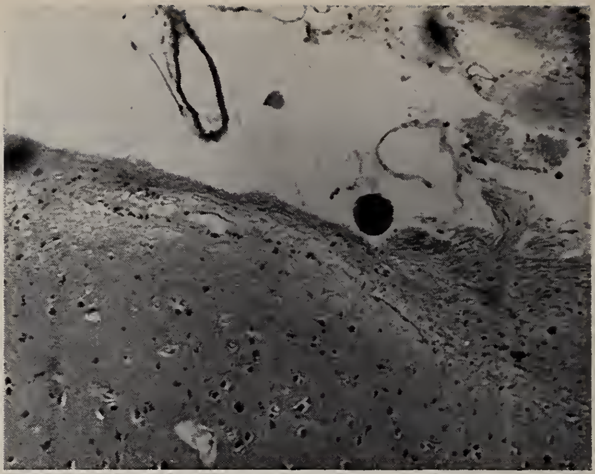

Figure 3.—Photomicrograph of a meningeal arteriole showing complete destruction. (Hematoxylin and eosin, x 100.)

voltage was less on the right. No definite areas of focal slowing or epileptiform discharges were noted. The interpretation was a slightly diffusely abnormal record with some asymmetry. Pneumoencephalography showed minimal ventricular dilation, suggesting slight cortical atrophy. Cerebrospinal fluid at that time showed protein content of 40 mg and sugar of 70 mg per 100 ml, and no cells. A brain scan, and x-ray films of the skull and sinuses were all within normal limits.

By 21 August the patient was alert and oriented, with no neurological residua.

She was readmitted on 30 September 1966 for control of erratic blood sugar. She had a transient episode of hallucinations and delirious behavior during a period of continuous documented 2+ to 4+ glycosuria with negative acetonuria. After subsequent readmissions to this hospital, she was sent to a nursing home and died 21 February 1967. Exact details were not learned although the terminal illness was thought to be due to ketoacidosis.

At autopsy, the brain weighed 1,148 grams. It was moderately atrophic, and the sulci were widened. All vessels at the base of the brain were thin, delicate and free of atheromata. The leptomeninges were thickened and blurred. There was no gross softening. Upon sectioning, rare punctuate 1 mm cystic areas were found. There was diffuse yellowish discoloration of the basal ganglia and substantia nigra. Microscopic study of hematoxylin and eosin stains revealed widespread neuronal destruction. There were diffuse small vessel subintimal proliferative and occlusive changes with siderocalcinosis. Scattered calcification, especially in the basal ganglia, and increase of microglial elements were evident (Figures 1, 2 and 3).

Comment

The initial acute episode of bizarre inappropriate behavior in this case remained unexplained clinically as did the later transient spells of hallucinations. Similar observations in a larger group of patients prompted Ives to speculate on the existence of a "special metabolic factor" in poorly controlled diabetics, predisposing them to mental instability.[4]

The profound comatose state and hemiparesis on 16 August could have been a manifestation of cerebral edema secondary to ketoacidosis as recently described by Young and Bradley,[5] although she recovered without receiving the appropriate therapy for cerebral swelling. Alternatively, one could invoke the very likely possibility of the ketoacidotic state leading to altered cerebral blood flow and metabolism, to be discussed further,[6] and also to a diminished effective circulatory volume, with resultant unmasking of a previously subclinical vascular lesion. Nonetheless, a transient impairment of brain function with focal features certainly suggests a vascular disorder, if not postictal in nature.

Case 3. A 32-year-old Caucasian woman who had had diabetes since age ten was taking 15 units of Lente insulin daily at the time of first admission, 31 January 1967. She had chronic renal failure due to diabetic glomerulosclerosis, was hypertensive and was overtly psychotic. She was confused, agitated and lethargic. Blood pressure was 202/108 mm of mercury. Optic disc margins were blurred. Deep tendon reflexes were active and equal except for diminished ankle jerks and there were no pathological reflexes. Blood sugar was 95 mg per 100 ml, serum acetone negative at no dilution, blood urea nitrogen was 90 mg per 100 ml and electrolytes were within normal limits. On 2 February she was disoriented, had horizontal nystagmus and a right Babinski reflex. Muscle tone, strength, and range of motion were all normal. The impression at this point was of toxic encephalopathy. Lumbar puncture revealed an opening pressure of 205 mm of water, with clear fluid containing no cells, protein 56 mg per 100 ml, and sugar 72 mg per 100 ml. A skull x-ray series and a brain scan were within normal limits. An electroencephalogram showed a disorganized background with widespread irregular 4 to 7 cycles per second theta activity and occasional bursts of 0 to 3 cycles bilateral synchronous frontal delta activity and no focal slowing—phenomena consistent with metabolic encephalopathy.

The patient was discharged 11 February 1967 and readmitted two days later with continuous focal seizures, head and eyes deviated to the left, jerking clonic movements to the left, reacting to pain and moving all extremities. A left Babinski reflex was present. Deep tendon reflexes were unchanged. Blood pressure was 220/114 mm of mercury. Blood sugar was 950 mg per 100 ml, sodium 125 mEq, potassium 3.5 mEq, chloride 77 mEq, and bicarbonate 20 mEq per liter, blood urea nitrogen 65 mg per 100 ml, and urine negative for ketones.

The seizures were finally controlled with intravenous paraldehyde after amobarbital failed. Treatment with fluids and a total of only 50 units of regular insulin corrected the blood sugar to 79 mg per 100 ml within 12 hours, at which time she was alert and oriented with no neurological deficit other than the preexisting peripheral neuropathy. After numerous simultaneous blood and urine sugar determinations, she was discharged taking 7 units of regular insulin and 10 units of NPH insulin daily. The blood pressure upon discharge was 200/100 mm of mercury.

During the interim, she was treated with antihypertensive and diuretic drugs by her family physician.

She was readmitted for the third and last time on 27 March 1967, after being found unconscious. Blood pressure was 240/140 mm, temperature 97°F, and pulse 110. There was bilateral papilledema with no nuchal rigidity. Extremities had normal tone and no obvious weakness. Deep tendon reflexes were unchanged. Cranial nerves II to XII were intact, and painful stimuli elicited a withdrawal response. Blood sugar was 58 mg and blood urea nitrogen 90 mg per 100 ml, electrolytes within normal limits. The urine was negative for sugar and acetone.

Fifty ml of 50 percent glucose solution by rapid intravenous infusion elicited no response. Treatment consisted of reserpine, intravenous nitroprusside and intramuscular dexamethasone for probable malignant hypertension with cerebral edema. The next day the Babinski sign was present bilaterally and the head and eyes deviated to the right. On lumbar puncture, opening pressure was 420 mm of water, and closing pressure 290 mm. The fluid was clear and colorless. Protein content 44 mg and sugar 100 mg per 100 ml. Three cells were present. Cultures were subsequently negative for fungi and bacteria. Blood pressure ranged from 220/100 to 160/70 mm of mercury during treatment.

On 30 March the patient responded to deep pain but was otherwise obtunded. Three days later, blood pressure was 230/130 without nitroprusside therapy and the patient was responding verbally. By 5 April she was alert and eating but her behavior was bizarre and inappropriate. Blood pressure at this time was 240/130 mm. Reexamination disclosed blurred optic discs bilaterally with no paresis or abnormal plantar responses. Lumbar puncture revealed an opening pressure of 196 mm of water, closing pressure of 206 mm (fluctuating with respirations), and clear fluid. Electroencephalography was essentially unchanged from the previous study. A brain scan was normal. Because of wide swings in blood sugar, treatment consisted of 5 units of regular insulin every eight hours.

For two to three weeks thereafter, the patient remained alert and oriented to name and time but was generally uncooperative and frequently refused even minimal nursing care. She became ambulatory and occupational therapy was begun when, on 24 April, after arising, she fell on her way to the bathroom. She was minimally responsive, her pupils were non-reactive, gaze was disconjugate, and bilateral papilledema was noted. Left hemiparesis and left Babinski reflex were evident. The left patellar reflex was exaggerated. The following day she could answer questions, and she ascribed her fall to a dizzy spell. Blood pressure was 220/100 mm.

She was generally irritable and lethargic and was unable to cooperate with visual field testing but it was noted that no blink was elicited by a threatening stimulus on the left. The corneal reflex was diminished on the left side and there was a left facial sagging. All cranial nerves were otherwise intact. Strength was decreased on the left side. Left-sided hyper-reflexia, a left Hoffman's reflex, and a positive snout reflex were present.

A subdural hematoma was considered. Lumbar puncture revealed an opening pressure of 390 mm of water, closing pressure 250 mm, fluid slightly turbid and xanthochromic, with 10,500 red cells and 10 white blood cells (all lymphocytes) per cu mm, chloride 123, sugar 162 and protein 225 mg per 100 ml. A gram-stained specimen was negative, and a culture was reported as containing a few diphtheroid colonies, most probably a contaminant.

A brain scan and skull series were normal. Electroencephalography revealed generalized disorganization with no localizing findings. The patient responded verbally to painful stimuli on 27 April and her blood pressure continued in the 240/120 range on a combined regime of Apresoline, Aldomet and thiazides. Her condition gradually deteriorated, bilateral upper motor neuron signs and Cheyne-Stokes respirations developed and she was more obtunded. On 3 May a right common carotid artery arteriogram demonstrated cross-filling to the left intracerebral circulation and it was considered to be a normal angiogram except for slightly enlarged ventricles. Subsequent spinal fluid cultures were all sterile but because of a continued polymorphonuclear leucocytic response on repeat lumbar punctures, treatment with ampicillin was added. The patient died 19 May without regaining consciousness. Autopsy was not permitted.

Comment

On the first and third admissions to the hospital, the patient initially was observed to have confusion, agitation, disorientation or obtundation. Transient cerebrovascular insufficiency, with or without cerebral edema, superimposed on mild cortical atrophy due to angiopathy, seemed likely. Initial transient improvement during the last stay in hospital was attributed to anti-hypertensive therapy, yet clinical improvement continued despite return of blood pressure to original levels and minimal funduscopic changes after therapy. The diagnosis of malignant hypertension is tenuous.

Her second acute episode was possibly on a hyperosmolal basis, with focal seizures as the initial clinical manifestation.[7] Calculated osmolarity* was 308 mOsm without correction for serum water or concurrent hyperlipemia. Conceivably the presence of cerebral angiopathy might lower the "osmolal threshold" at which clinical signs appear.

Assuming that diffuse small vessel disease existed, the terminal episode was undoubtedly an isch-

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*Calculated osmolarity $= 1.86 \text{ serum } (\text{Na}+) + \frac{\text{blood glucose}}{18} + \frac{\text{blood urea nitrogen}}{2.8}$.

TABLE 2.—*Data on Three Patients with Cerebral Syndromes of Diabetes Mellitus*

Case No.	*Age at Diagnosis of Diabetes (Years)*	*Age at Death (Years)*	*Duration of Known Diabetes (Years)*	*Length of Survival After Initial Acute Cerebral Dysfunction*
1	5	22	17	7 months
2	11	41	30	6 months
3	10	32	22	3½ months ??

emic or hemorrhagic lesion in the right internal capsule, with the resulting hemiparesis causing the fall rather than resulting from it. Postural hypotension due to prolonged recumbency might have initiated the final sequence of events.

Discussion

The acute cerebral syndromes of diabetes mellitus have included cerebrovascular disease, hypoglycemia, infections, hyperosmolality, and neurological changes associated with ketoacidosis.[8,9,10] DeJong,[11] describing a patient similar to ours, recognized the increasing incidence of recurrent focal and diffuse cerebral disease, especially in younger diabetic patients. He correctly attributed this to accelerated atherosclerosis and arteriosclerosis. Atherosclerosis is almost inevitable in long-standing diabetes, yet there has been a disparity between the findings of arteriosclerosis and diabetic small vessel involvement in general.[12] Studies of intracerebral vessels by light microscopy usually have not revealed a consistent histological picture,[13-15] but this could be due to random patient selection. In one large series, however, proliferative lesions of the smaller cerebral vessels were repeatedly demonstrated.[15] Reske-Nielsen and coworkers,[1,16] in Denmark, studied the brains of 16 patients with juvenile diabetes who died in early adulthood and found leptomeningeal thickening, basal ganglia calcification and diffuse cerebral degeneration to some extent in all specimens. Vascular changes, ranging from nodular intimal thickening of arteries with disruption of the internal elastic lamina to basement membrane thickening of capillaries, were a constant feature. They concluded that their neuropathological findings, while not specific, were unlike those seen in any other condition and therefore proposed the use of the term "diabetic encephalopathy." They felt, however, that the degree of damage found was too severe to have been due solely to the angiopathy and mentioned the likelihood of a primary diabetic abnormality of brain tissue, a concept already applied to diabetic peripheral neuropathy.[17,18]

The pathological findings in Case 2 reported herein are almost identical to those in the 16 patients and also similar to those in the 28-year-old man described by DeJong.[11] Question arises as to the frequency of this aspect of diabetes, since this is apparently a rare complication, according to the American literature,[11,14] as contrasted with the experience of the group from Denmark.[1,16] Similar gross pathological features were seen in tuberculous arteritis and meningovascular lues many years ago.

Our three patients had much in common (Table 2). All had had labile diabetes since childhood, with a tendency for wide fluctuations of blood glucose, requiring frequent adjustments of insulin dosage, and with severe vascular concomitants of the diabetic state. Each had a rapid remission to her previous state of health with no neurological residua despite profound focal or diffuse neurological dysfunction. Conceivably, episodic embolic showers from undetermined foci, transient ischemic attacks and recurrent small vessel thromboses might all result in a similar clinical picture. Retrospective study of each patient's clinical course, however, suggested something more than diverse manifestations of uncomplicated atherosclerotic cerebrovascular disease alone, and numerous pathophysiologic problems certainly coexisted.

The rapid downhill course of all three patients within a seven-month period indicates an ominous prognostic pattern despite the neuropathological differences. Diabetic cerebral angiopathy, in association with other pathophysiologic alterations of the diabetic state, (vide infra) offers the most likely explanation in at least one of our patients. Therefore, pending further reports, we wish to add diabetic vascular encephalopathy tentatively to the list in Table 1.

Changes in mental status during ketoacidosis cannot be correlated with blood pH, pCO_2 or electrolyte derangements. There has been some relationship with total blood ketones and, more importantly, acetoacetic acid.[6,19] Cerebral oxygen consumption is, however, uniformly depressed (below 2.1 ml of O_2 per 100 grams of brain tissue per minute) during ketoacidotic coma. This is not due to diminished oxygen delivery to the brain since cerebral blood flow is slightly elevated in those ketoacidotic patients who are unconscious (65 ml per 100 grams of brain tissue per minute as compared with 54 ml for normal controls). This decreased oxygen utilization during coma is probably due to a combination of factors such as amount of ketones and degree of acidosis, but whether coma is the result of an inability of the brain to extract and utilize oxygen or is the cause of the poor oxygen uptake is not apparent from these data.[6]

Recent evidence reported by Posner and Plum relating mental status to type of acidosis is pertinent. They found that spinal fluid pH was maintained within a near normal range during severe metabolic acidosis in those with unimpaired mental function while the same degree of pH change in respiratory acidosis caused a decided lowering of spinal fluid pH with associated unconsciousness.[20] The almost immediate diffusion of carbon dioxide across the blood-brain barrier as contrasted to the slow movement of hydrogen and bicarbonate ions offers some explanation for the above findings, as well as the possibility of an altered active transport for bicarbonate induced by acidemia. Thus, if a ketoacidotic patient is unconscious when first seen, one might consider a prolonged duration of ketosis, leading to gradual lowering of spinal fluid pH, after careful exclusion of other causes as already listed above. Much more frequently, one sees an increased lethargy and dullness in the course of treatment of ketoacidosis, especially when intravenous bicarbonate is administered.[20] Acutely raising serum bicarbonate levels would not be expected to alter spinal fluid bicarbonate concentration and if ventilation diminished in response to the resultant abrupt increase in blood pH, a state of relative hypercarbia would exist in the spinal fluid alone, lowering the spinal fluid pH.

Along these same lines, any decrease in hyperventilation with beginning signs of depressed sensorium is cause for alarm. We recently observed this phenomenon in a 19-year-old girl with severe ketoacidosis, beginning one to two weeks previously, who probably had hypokalemic paralysis despite aggressive replacement of potassium (400 mEq of KC1 intravenously over 12 or 14 hours) in the course of treatment, with resultant hypoventilation and coma. We reasoned that since the serum K+ had not increased relative to the repletion of intracellular stores, a state of hyperpolarization existed. In any event, mechanical ventilatory assistance, as guided by bicarbonate and pCO_2 levels in both blood and spinal fluid, offers a rational approach to this unusual complication during correction therapy in ketoacidosis.

Hypoglycemia as a contributing factor, not well documented in our patients at the time of admission, cannot be totally excluded,[8] the lack of response to rapid intravenous glucose notwithstanding. Reactions usually associated with insulin hypoglycemia may occur in labile diabetics at a time of relatively high blood sugar levels.[21] The combination of inapparent fluctuations of blood glucose and the appropriate vascular setting can result in disordered (possibly reversible) neurological function, dependent upon location, level of function, and a host of other as yet undefined factors.[8,22] Electroencephalographic evidence may not be helpful in this regard since hypoglycemia severe enough to cause symptoms has been associated with a normal tracing[8,21] and about half of patients with labile diabetes have abnormal recordings anyway.[23]

Blood viscosity is, on the average, 20 percent higher in diabetic persons than in normal controls[24] and, since flow is inversely related to viscosity, this may have been an additional predisposing factor for transient cerebral dysfunction unique to this group.

The occurrence of cerebral dysfunction in young diabetic patients is decidedly less frequent than other organ involvement.[25] Perhaps, as has been suggested for diabetic retinopathy,[26] accelerated small vessel disease is time-dependent. The premature death of the juvenile diabetic from cardiorenal failure might preclude the eventual development of the above described vascular encephalopathy.[25] This seems to be an adequate explanation for the relative rarity of this problem, despite the prolongation of life attendant upon the widespread use of insulin since 1922. Increasing use of hemodialysis and renal cadaver homotransplantation as a mode of therapy for terminal diabetic glomerulosclerosis, as most surely will come about, may be expected to reverse this trend.

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DRAINAGE FOR PATIENTS WITH LIVER INJURY

"[For effective drainage in patients with acute injuries of the liver,] drains should be properly placed and of a suitable type. The familiar Penrose drain tends to kink and to lose its effectiveness. To ensure continuous drainage, there is nothing as effective as the now familiar sump drain whose air vent ensures continuing patency. A variety of these have been devised, and several are commercially available. They can be easily improvised by passing a small plastic tube through a larger rubber drainage tube. Madding made the ingenious suggestion that a sump can readily be obtained simply by cutting off the balloon of a Foley catheter. Norton Waterman . . . at the University of Louisville devised a particularly effective mechanism for pancreatic drainage by placing a sump which he improvised with two catheters within a fenestrated Penrose tube. We have found this to be equally effective in drainage of the liver; and we like it better, as a matter of fact, than any of the commercial sumps.

"Whatever the type of drain selected, it is important to provide adequate wounds of exit, preferably in a dependent site apart from the operative incision. An incision length of one to one and a half inches, or a size admitting two fingers, is a good rough guide as to the proper size."

—Rudolf J. Noer, M.D., Louisville, Kentucky
Extracted from *Audio-Digest Surgery,* Vol. 15, No. 21, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

Dupuytren's Contracture—Etiolo

JAMES R. DOYLE, M.D., *San Francisco*

■ *Although Dupuytren's contracture was first described more than 300 years ago, the cause is not yet certainly known. It is only agreed that the disease process affecting the palmar fascia is most commonly found in older-aged males of Caucasian descent.*

Conservative or non-surgical treatment is usually ineffective. Surgical treatment includes fasciotomy, partial fasciectomy and total fasciectomy. Fasciotomy is indicated for localized disease or for patients with medical conditions which preclude more extensive operation. Subtotal fasciectomy with or without skin graft is the most commonly employed procedure. Total palmar fasciectomy is seldom indicated. Improved function of the hand can be anticipated after adequate surgical intervention.

d Principles of Treatment

PULVERTAFT AND REID in 1963 stated: "It is humbling to reflect that although Dupuytren's disease has been known since the description by Plater (1614), Astley Cooper (1822) and Guillaume Dupuytren (1832) the cause remains obscure and there is no general agreement as to the ideal method of surgical treatment.[1-3] Dupuytren, although historically preceded by Clive in 1808 and Cooper in 1822 in the recognition of the fascial origin of the disease, was the first to perform an operation for relief of the contracture.[4,5]

Etiology

The exact cause of Dupuytren's contracture is unknown. Predisposing factors which are universally accepted are age, sex, race and heredity.[4] Dupuytren's contracture is observed most often in the fifth through seventh decades. There are occasional occurrences in the third and fourth decades and very rare occurrences in the second.

Dupuytren's contracture is a disease of men. Most reported series indicate that the disease occurs seven to eight times more frequently in men than in women.

Most investigators agree that this disease is much more common in the non-pigmented races and is uncommon in Chinese.

Larsen noted that there is a definite hereditary tendency toward the development of the disease and states that European writers frequently report as many as one-third of their patients with Dupuytren's contracture have a positive family history.[5]

The role of trauma in the development of this disease is one of the major points of disagreement among surgeons treating this problem. Clarkson in 1961, in a survey of numerous authorities, found that most opposed the view that a direct relationship existed between trauma and Dupuytren's disease.[6] There was some opinion, however, that trauma to the medial side of the palm followed by fixation of the digits in flexion might represent a causal relationship to the precipitation or aggravation of the disease. Many historical studies, including those of Early, Herzog and Hueston, failed to show any occupational connection with chronic trauma.[7-9] In contrast, there has been a significantly high, but as yet unexplained, incidence of Dupuytren's disease noted among brewery workers, alcoholics, and epileptics.[9,10]

The Palmar Fascia[11,12]

The palmar aponeurosis forms the volar wall of a space that contains the flexor tendons, the lumbrical muscles and the vessels and nerves of the palm. Proximally it is joined to the palmaris longus tendon, or if the tendon is absent, to the forearm fascia. In the distal half of the palm septa pass into the depths of the palm between the tendons of the adjacent fingers. These vertical septa join the deep palmar fascia and thereby form arcades. Eight such arcades are formed with each alternate tunnel transmitting a lumbrical muscle and digital vessels and nerves; each of the other four tunnels transmit a pair of flexor tendons.

Near the heads of the metacarpals a transverse ligament is prominent which spans the space between the four main longitudinal bands. These

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Submitted 20 December 1968.
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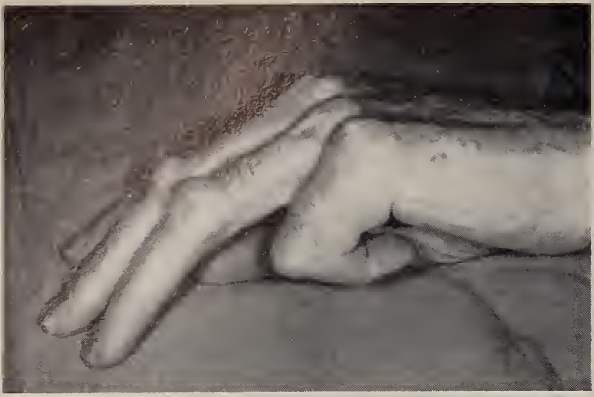

Figure 1.—Hand of 45-year-old man with decided flexion deformity of the little finger. Note the prominent knuckle pads over the proximal interphalangeal joints of the ring and middle fingers. The fixed flexion contracture of the proximal interphalangeal joint of the little finger was arthrodesed in 45° of flexion after excision of the diseased fascia in the palm and digit.

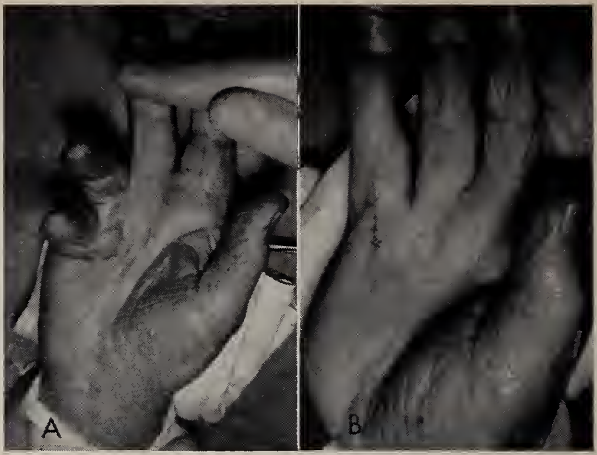

Figure 2.—(A) The patient, a 70-year-old man, had pronounced flexion deformity of the little and ring fingers. (B) Simple fasciotomy under direct vision produced remarkable improvement. The longitudinal incision provided for early motion without separation of the wound.

longitudinal palmar bands pass into the superficial digital fascia and the vertical septa pass into the deep digital fascia. These fibers from the palm which pass into the fingers ultimately attach to the sides of the proximal and middle phalanges and thereby account for the proximal interphalangeal joint contracture which may occur.

Clinical Features

The Dupuytren's lesion may become manifest in a variable manner; it may be noted to be only a small palmar nodule or it may be complete contracture of the ring and little fingers which are firmly opposed to the palm. The palmar nodule represents the first manifestation of the disease in the palm and, although progression is usually noted beyond this stage, it is entirely possible that the nodule may not progress to involve the remainder of the palm or digital fascia. If progression occurs, thickening of the palmar fascia on the medial side of the hand is noted with associated flexion contracture at the metacarpal phalangeal joint. Further progression of the disease is often associated with a flexion deformity at the proximal interphalangeal joint. The ring finger is most commonly involved with the little finger being the next most commonly involved.[13,14]

Dupuytren's knuckle pads may be noted over the dorsal aspect of the proximal interphalangeal joints. Skoog noted their presence in 44 percent of patients with Dupuytren's contracture.[15] These nodular subcutaneous masses are illustrated in Figure 1.

Progression of the disease may be variable and the surgeon must recognize this fact. Moreover the patient should be told, before any surgical intervention, that the disease which has affected his hand or hands is one that is characterized by chronicity and recurrence. This is easily understood in that the palmar fascia is an extensive tissue involving the entire palmar area with extensions into the proximal phalanx of each of the fingers. Although partial excision of the fascia may be performed, residuals of palmar fascia remain and may represent sites for future involvement with disease. Hueston noted that in spite of complete excision of palmar fascia and abnormal tissue, recurrence is common in patients who were operated upon during the phase of rapid progression of the disease.[9] The fact that nodules or recurrent Dupuytren's disease may develop in an area previously operated upon indicates, in Hueston's opinion, that these recurrent nodules could not have arisen from any preexisting anatomical fascial bands but developed from the normal fibro-fatty tissue remaining in the region.

Treatment

Larsen observed that non-operative treatment of Dupuytren's contracture with local injections of pepsin, fat solutions, fibrinolysin, copper sulfate, and pancreatic extract and cortisone have had no effect upon the disease. Treatment with oral tocopherol may produce temporary softening of the contracture but the progressive course of the disease is not altered.[16] Although Finney suggested a combination of preoperative irradiation and surgery for advanced cases, Larsen observed that the

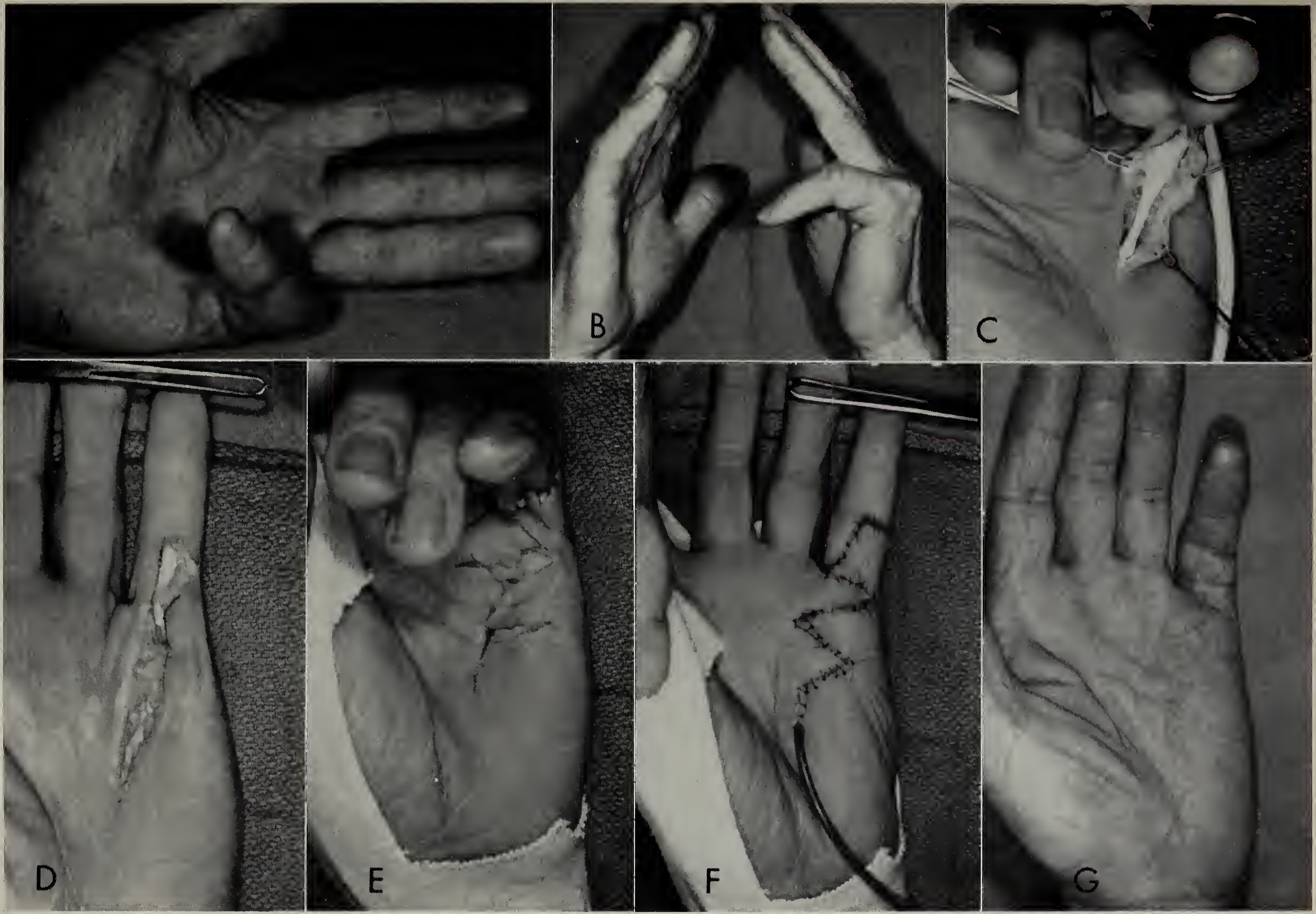

Figure 3.—(A and B) Hand of 50-year-old man with isolated disease involving the fifth ray. A single "cord" of hypertrophied fascia passed from the proximal palm into the proximal interphalangeal joint of the little finger. Maximum extension is demonstrated in B. (C) A longitudinal incision was used to expose and excise the diseased fascia. (D) Note the normal fat and underlying flexor tendons after excision of the fascia. (E and F) Z-plasty closure was performed as noted. The drain (F) is considered essential. (G) The cosmetic and functional result is considered to be good.

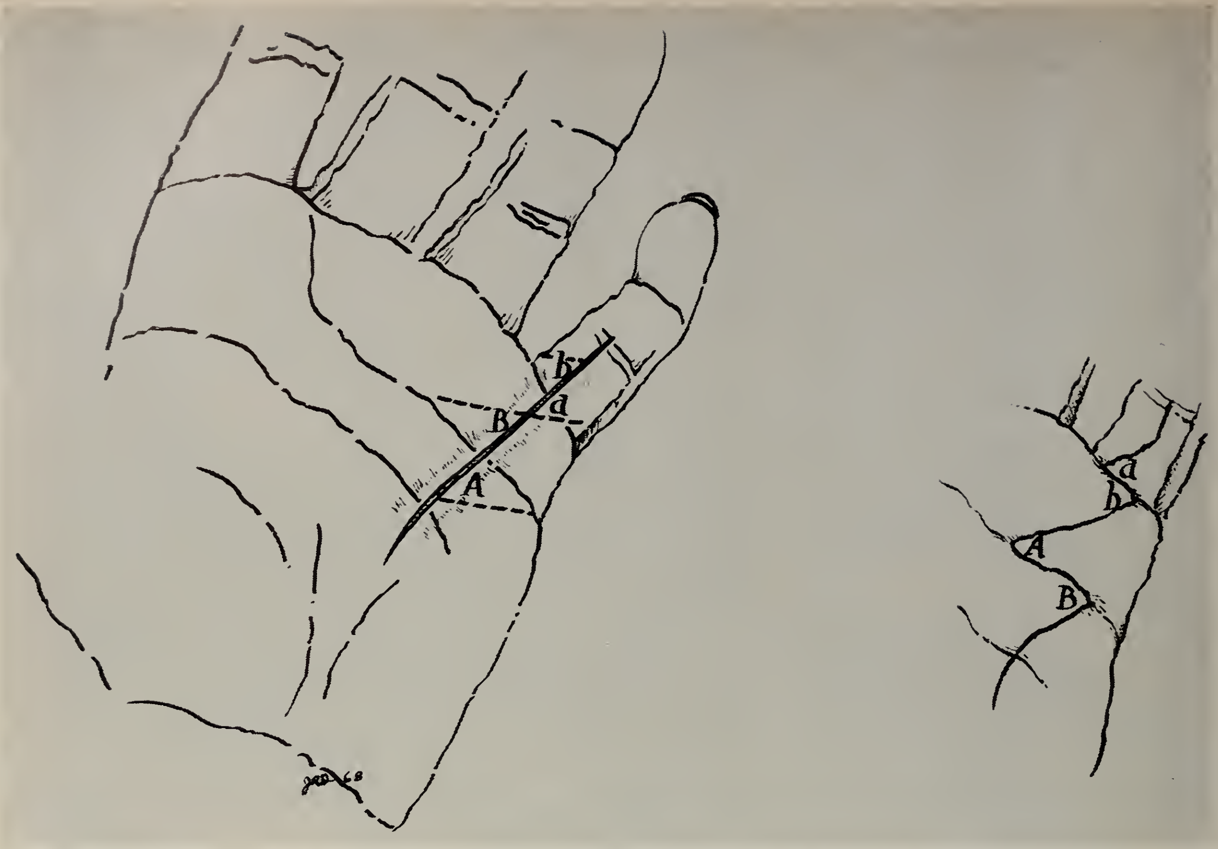

Figure 4.—Z-plasty: The longitudinal approach provides for direct exposure with a minimum of soft tissue undermining. A longitudinal incision in this area, if allowed to heal, would produce recurrent flexion deformity because of the longitudinal scar which crosses two flexion creases at right angles. Accordingly, the Z-plasty is used to break up this line of tension. In addition, the Z-plasty technique provides for longitudinal lengthening of contracted skin.

results were less satisfactory than might be expected from surgery alone.[16,17]

The majority of physicians dealing with this process agree that the most effective treatment is surgical. Operation is by no means indicated in all cases of Dupuytren's disease. When the contracture interferes with function or occupational requirements, surgical treatment is indicated. The aims of operation are to correct or partially correct the relatively fixed flexion contractures involving the affected digits.

Unfortunately it is impossible to forecast accurately the probability of progression of the disease. Mild disease which remains static does not warrant operation. However, such early operation is technically easier and the results are better. Conversely, long-standing contracture is often associated with permanent joint changes and a perfect result is unlikely. A few months' observation may answer the question regarding the need for operation. If the contracture progresses rapidly, surgical correction is recommended. If it remains static (and the deformity is mild) operation is not indicated.

The operation must be designed to fit each patient. Age, general health and functional needs must be considered. Postoperative joint stiffness is the major complication of operative treatment,[18] particularly if arthritic changes are already present. Similarly, a thick broad hand does not withstand extensive surgical intervention and is prone to postoperative stiffness.

The three main forms of surgical treatment are fasciotomy, partial fasciectomy and a complete or radical fasciectomy. Fasciotomy may be the procedure of choice in older persons whose general medical condition precludes more extensive operation. It can be performed under local anesthesia and is a practical answer for limited and relatively isolated bands of contracted fascia. Fasciotomy may also be used as a preliminary procedure in severe contractures in preparation for more radical procedures. The surgeon may be surprised to note the pronounced functional gains from this relatively simple procedure. Longitudinal incisions are advocated, since they permit early motion without gaping of the wound. The contracted band is iso-

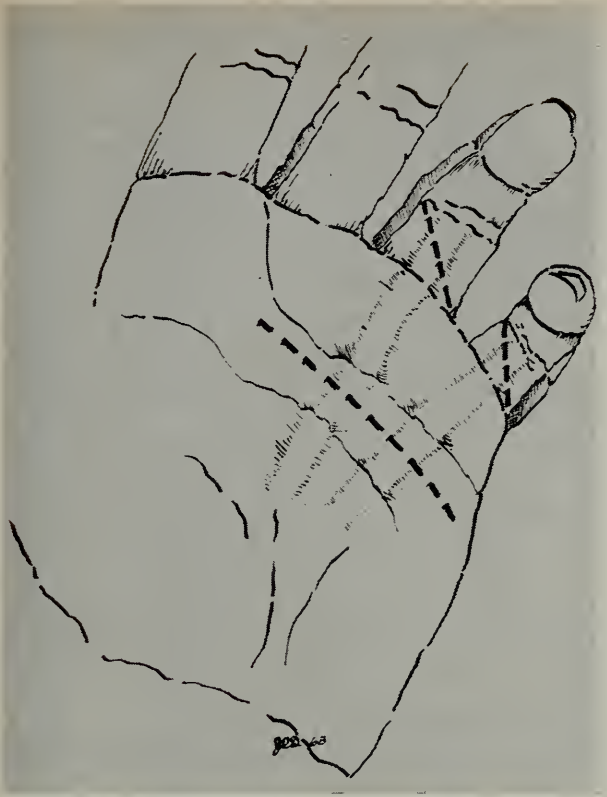

Figure 5.—The transverse palmar incision is used if extensive disease is noted in the palm. It is supplemented with digital incisions as needed.

lated and sectioned under direct vision with a scalpel. Blind sectioning of such bands may result in inadvertent transection of nearby vessels or nerves (Figure 2).

Partial fasciectomy is the most commonly employed technique and involves excision of the diseased fascia in the palm and fingers. It must be observed that the contracted fascial bands originate in the palm but extend into the proximal phalanx and across the flexor and lateral aspect of the proximal interphalangeal joint. Surgical exposure must therefore be directed toward the palm and the proximal phalanx. If a single longitudinal band is present, it may be exposed through a longitudinal incision which is closed by a Z-plasty (Figures 3 and 4). If the disease process is more extensive, a transverse palmar incision and oblique digital incision may be used for good exposure (Figure 5). A surgical tenet as regards incisions is to design the incision so that all diseased fascia can be removed with a minimum of dissection. Obviously, each hand must have incisions which meet its particular requirements.

It is the author's opinion that, anatomically, total fasciectomy is seldom indicated and that the surgical approach to Dupuytren's disease should be that of relatively total excision of all diseased palmar fascia including digital extensions. This may result in relatively localized operation with the understanding that recurrences may occur in areas which were not previously involved. It must be remembered that the remaining fascia has potential for hypertrophy.

Cases of long-standing contracture are often associated with contracture of the skin in the palm. In addition, some cases of severe Dupuytren's disease manifest infiltration of the skin so that the disease process cannot be excised without leaving a very thin layer of skin in some areas. If extremely thin or excessively traumatized skin remains following fasciectomy, it may be necessary to replace the skin by a skin graft. On many occasions, after complete excision of the diseased fascia a large gaping wound will be observed in the palm or digits with passive extension of the fingers. Primary closure of these wounds would result in a considerable flexion deformity of the fingers and it is the author's opinion that this flexion deformity can be prevented by the insertion of a full thickness skin graft into the defects (Figure 6).

During dissection it is extremely important to carefully identify the digital arteries and nerves in order to avoid injury to them. This is especially important in the proximal phalanx where the nerves may be very close to the digital fascial bands. Extensive undermining should be avoided. The studies of Conway have demonstrated that the arterial supply of the palmar skin is in a mosaic fashion and that skin necrosis is likely to follow the wide and indiscriminate undermining in the palm.[19] It is the author's custom to drain all the operative wounds by the use of a sterile No. 8 (French) red rubber catheter. The tip of the catheter is passed through the proximal portion of the incision and down to the distal area of dissection. The catheter is relatively small and is well tolerated by the tissues. After closure of the skin, the catheter is coiled on the flexor surface of the wrist and can easily be removed in 48 hours without disturbing the primary compression dressing.

Certain digits, especially the little finger, often are associated with extreme degress of contracture and the need for amputation of this digit is often entertained. This is especially true when the deformity is long-standing and is fixed. Although an amputation is easily performed and the cosmetic

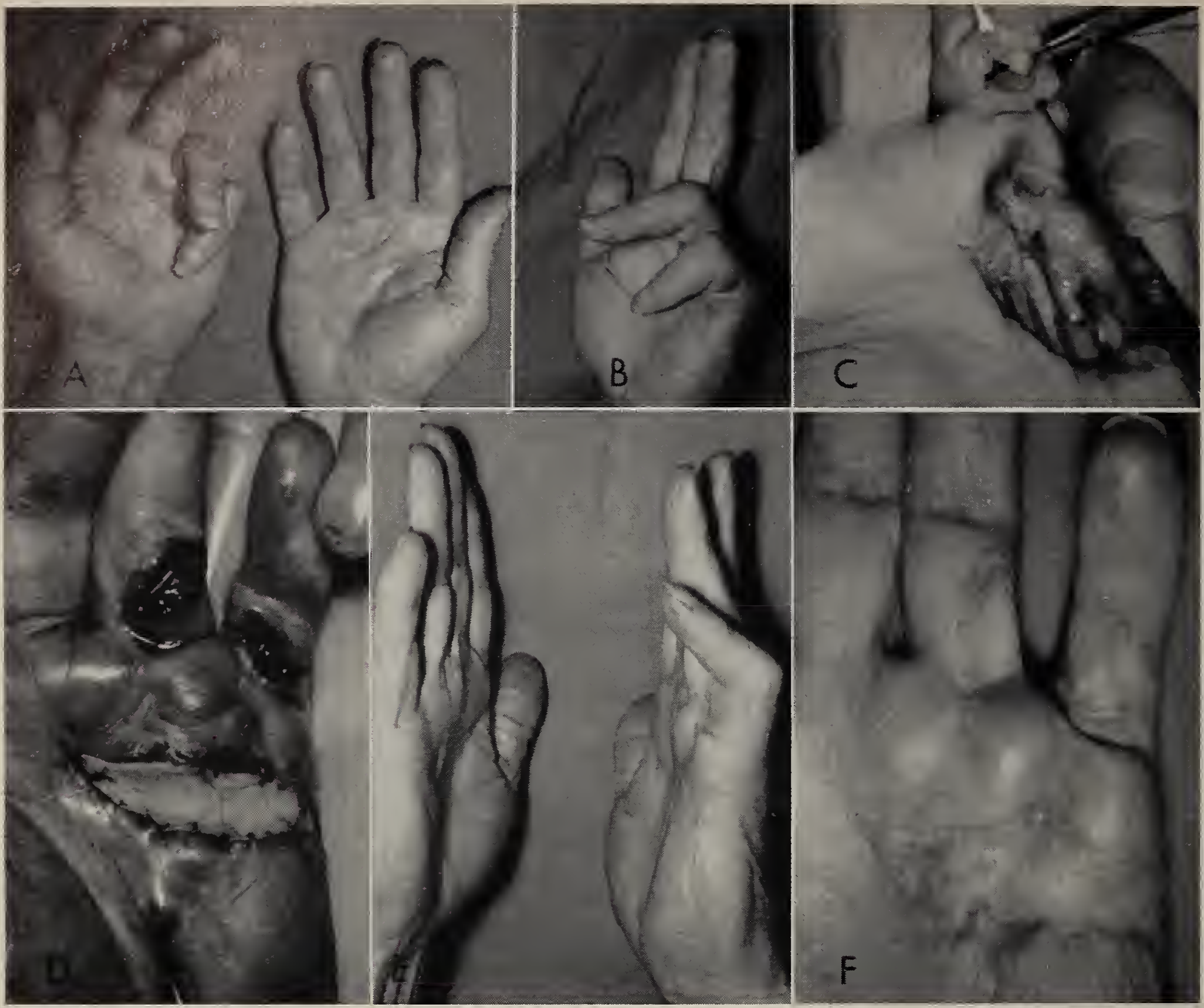

Figure 6.—The patient was a 45-year-old man. (A and B) Note the decided flexion deformity of the ring and little fingers of the left hand. (C and D) Palmar and digital incisions were used to excise all diseased fascia. The resultant skin defect in the palm required a full thickness skin graft. A similar graft was placed in the defect in the little finger. Primary closure of these wounds would have resulted in early recurrence of the flexion deformity. (E and F) The result is considered to be very satisfactory.

and functional results are not unreasonable, many surgeons hesitate to perform this practical solution. Amputation is especially recommended in long-standing cases of fixed flexion contracture of 90 degrees or more which involve both the proximal interphalangeal and the metacarpal phalangeal joints.

Fixed flexion contracture of 90 degrees or more of the proximal interphalangeal joint is a most difficult problem to resolve. Long-standing contracture is associated with contracture of all surrounding soft tissues and even extensive dissection and surgical release cannot effect permanent changes. Forced extension at the operating table, if associated with subluxation of this joint, predicts recurrence of the deformity in the author's experience. When such irreparable joint changes are encountered, the best and most lasting result is arthrodesis of the joint in 45 degrees of flexion. Two cases of this type were encountered in this series. The methods used by the author in fifty cases were as follows: Fasciotomy, 3; partial fasciectomy, 40; partial fasciectomy with skin graft, 6; amputation of digit, 1.

Local or distant pedicle flaps may be used to provide coverage when a large defect results from adequate excision of the diseased palmar fascia and skin.[20] The filleted skin of an amputated little finger certainly provides an ideal flap for this purpose. Less ideal are the chest or abdominal pedicle flaps and the least desirable is the local flap which is obtained by rotating a dorsal hand flap into the palm.

The dressing applied immediately following operation is of great importance. One of the most disastrous complications which can occur following excision of Dupuytren's contracture is the occurrence of a hematoma in the palm. Such a hematoma results in devitalization and compromise of the blood supply to the palmar skin and may result in necrosis of the skin. In the author's experience, a hematoma can be prevented by pre-closure hemostasis and adequate drainage with the previously described catheter. In addition, the dressing must be of a moderate compression type with several fluffs of gauze placed on the palm and on the dorsal surface of the hand and fingers. The dressing extends from the fingertips to the wrist. The thumb is allowed to remain out of the dressing and acts as a stabilizing post to prevent migration of the dressing. Sponge rubber or a synthetic variant of at least one-inch thickness is placed in a "pancake" fashion on the palmar and dorsal surfaces of the hand and fingers. This is firmly wrapped into place with bias-cut stockinette bandage which further adds to the gentle compression. The author is of the opinion that the fingertips should be splinted in this fashion in as much extension as the soft tissues will tolerate.

The objectives of treatment include correction of a flexion contracture and temporary extension of the fingers for seven to ten days has been observed not to result in permanent stiffness in extension. It must be observed that the flexor tendons possess greater strength than the extensors, and this fact is responsible for recovery of flexion. During the first critical days, splinting the finger in extension prevents the protective attitude of flexion and in the author's experience has produced a better overall result as regards correction of the flexion contracture. Following removal of the dressings at seven to ten days, active finger exercise is started. Close supervision, encouragement and reassurance are mandatory during this phase of recovery. In cases in which joint contracture is a problem, stretching with a dynamic splint during this phase of recovery may be helpful.

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CLUSTER MIGRAINE

"The crux of the cluster migraine is that it is predictably unpredictable, and the effectiveness of any prophylactic treatment that you use will depend in general upon the time you use it. If you use it in the fifth or sixth week, and the series or the cluster lasts for six weeks, you'll be a hero until the headaches start 18 or 24 months later. If you use it in the beginning, you'll have a stormier period. They've been known to stop as suddenly and for as unexplained reasons as they occur."

—ARNOLD P. FRIEDMAN, M.D., New York City
Extracted from *Audio-Digest Otorhinolaryngology*, Vol. 1, No. 4, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

Management of Chron

GARY L. THOMAS, M.D., *Sacramento*

■ *Management of chronic middle ear effusion must center around the reestablishment of normal eustachian tube function. If fluid does not clear with medical management, aspiration becomes necessary. A prosthetic eustachian tube is placed in the tympanic membrane in order to artificially ventilate the middle ear space while primary etiologic factors are being corrected.*

Unless recurrent or chronic ear disease of this nature is diligently treated, progressive damage may bring about irreversible hearing loss and the potentially dangerous disease, cholesteatoma of the ear.

CHRONIC MIDDLE EAR effusion causes significant disability. Hearing impairment, feeling of fullness and plugged sensation involving one or both ears are consistent complaints. Autophony (the sensation of talking in a barrel), tinnitus, and occasional external otitis as a result of a patient's trying to clear his ear with his finger or a swab (Q-Tip®) not uncommonly compound the problem. Most adults will not tolerate this situation for more than a few days without insisting on vigorous therapy. Disability in children is just as great, although they do not express themselves as freely.

Diagnosis

When an air-fluid level is present and readily seen through a transparent tympanic membrane, the diagnosis is easy. Often, however, the tympanum will be completely full of fluid, giving a glassy or an opaque appearance to the tympanic membrane, with tiny, dilated vessels coursing over it. Sometimes the only apparent abnormality is an amber discoloration. In cases where diagnosis is not obvious, utilization of the pneumatic (Siegle's) otoscope is useful in demonstrating decreased mobility of the tympanic membrane and, occasionally, motion of an air-fluid level. It is helpful to rotate the light of the otoscope or the microscope into various positions, throwing a shadow onto the promontory through the transparent tympanic membrane. On this maneuver if the tympanum is filled with fluid one does not observe the normal translucency of the empty tympanum. Audiologic evaluation provides additional information, revealing up to 45 decibel conductive hearing impairment.

Etiology

The great importance of the eustachian tube function becomes apparent when one considers the thousands of people with normal eustachian tube physiology who tolerate rapid barometric pressure change, severe allergic rhinitis, severe upper respiratory infection, even a middle ear infection, without development of chronic middle ear effusion. Patients with poor eustachian function tolerate these same conditions without developing chronic middle ear fluid as long as there is a functioning prosthetic eustachian tube in the tympanic mem-

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Submitted 3 September 1968.

Presented in part before the Section on Laryngology, Otology, and Rhinology at the Annual Convention of the American Medical Association, San Francisco, 18 June 1968.

Reprint requests to: 5301 F Street, Suite 115, Sacramento 95819.

iddle Ear Effusion

brane, artificially ventilating the middle ear space (Figure 1). However, once the prosthetic tube extrudes or becomes occluded, chronic fluid frequently recurs unless the primary etiologic factors, such as allergy[1,2] or infection, have been corrected in the meantime. Recurrent, unilateral effusion involving the same ear each time is not uncommon, again suggesting an anatomic-physiologic abnormality of the eustachian tube in addition to the precipitating causative factor. The various etiologic factors become significant when the anatomic and physiologic nature of the eustachian tube is such that the compounded problems produce disease.

Mechanism of Fluid Production

One of several mechanisms may be involved in fluid production, depending upon the etiologic factor.[3] Pathologic changes may initially involve only the eustachian tube, or there may be direct involvement of the middle ear mucosa. Sometimes both factors are involved.

Effusion secondary to rapid barometric pressure change results from failure of the eustachian tube to ventilate the middle ear space adequately, with development of undue negative (rarely positive) pressure. This trauma causes vascular engorgement and, eventually, serous or serosanguineous transudate. Under the rapid barometric pressure change in a flight chamber, transudate may develop within a few minutes. This may occur in an otherwise healthy and well patient whose ear appeared normal before the barometric trauma.

Fluid formation occurs in much the same way from effusion secondary to edema of the eustachian tube caused by allergic reaction or respiratory infection. Oxygen, and later nitrogen, are absorbed by the mucosal lining of the middle ear and mastoid. Negative pressure results when the eustachian tube does not ventilate the middle ear properly. There may be no associated inflammation of the tympanic membrane, but only the appearance of fluid.

Allergic or inflammatory edema may directly involve the middle ear and mastoid mucosa. As the edema subsides, an excessive negative pressure occurs as a result of the swollen membranes having displaced air from these structures. Again there is an associated failure of the eustachian tube to ventilate the middle ear space adequately. Tissue reaction may also cause mucous gland hypersecretion, with excessive fluid production.

Some cases of chronic effusion following bacterial otitis media have, as an additional factor, chronic inflammatory edema caused by attenuated organisms. This may result from deficiencies in antibiotic specificity or dosage or duration of treatment.

Chronic effusion is commonly seen in patients who have faulty function of levator and tensor veli palatini muscles due to a paralysis or cleft palate,[4] including submucous cleft palate. These muscles are responsible for the active opening of the eustachian tube to ventilate the middle ear, and also control the velopalatine closure of the nasopharynx, preventing regurgitation of food during swallowing. A faulty function of these muscles results in inadequate ventilation of the middle ear, and often in the bathing of the eustachian tube orifices with milk or other food products, causing an irritative or allergic edema of the eustachian tube.

Management

Conservative

The goal in management of chronic middle ear effusion must center around reestablishment of normal eustachian tube function.[5-7] Inflammatory edema is reduced by the use of oral decongestants, such as phenylpropanolamine (Propadrine®). It is best to avoid topical decongestants, such as nose drops, nasal sprays or inhalers because of the re-

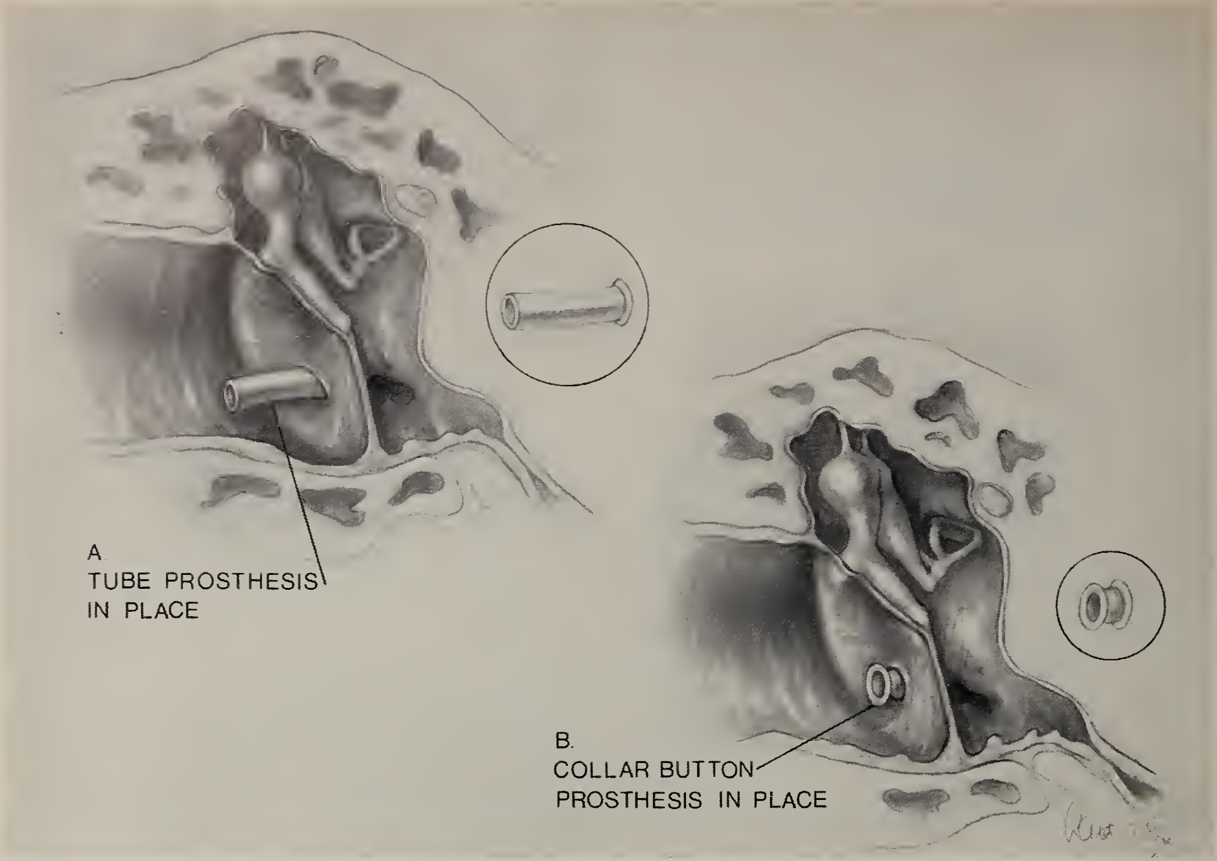

Figure 1.—Eustachian tube prosthesis ventilating middle ear space.

bound congestion which will occur. A vicious cycle of decongestion followed by congestion, necessitating the need for further decongestant, is quickly established and the patient's recovery is retarded.

Allergic factors are combatted with antihistamines and often the decongestant and antihistamine are combined in one medication.

Upper respiratory tract or middle ear infections are treated with antimicrobial agents, usually administered for a minimum of ten days.

Politzerization (inflation of the middle ear space by way of the nose and eustachian tube) appears to expedite the reestablishment of eustachian function and facilitate evacuation of fluid by displacement with air. This may be repeated as often as practical. Concern has been expressed that blowing infectious material from the nasopharynx into the eustachian tube might cause complications. This has not been a problem in our experience, but the procedure is frightening or disagreeable to some adults and to most children and the benefits do not justify coercion.

How long to continue conservative therapy depends upon circumstances. Adults are often unwilling to tolerate this situation for more than a few days to a week without aspiration. Ordinarily two weeks should suffice to determine whether or not aspiration is necessary. However, if hearing impairment and disability are mild, an even longer period will do no harm, provided the patient is reliable and will return for observation to make certain that fluid completely disappears. Frequently patients who have previously had aspiration for effusion will ask for this treatment immediately, knowing the pronounced improvement it brings.

Dealing with children is somewhat different, for they do not express themselves as freely about their disability. Also, general anesthesia is ordinarily required for aspiration in children. Hence they are often treated conservatively for about four weeks before aspiration is advised. The tenacious mucoid effusion, however, will rarely clear with medical management.

For either adults or children, if there is recurrent ear pain or recurrent purulent otitis media, as not uncommonly happens, treatment should be undertaken in a more urgent manner.

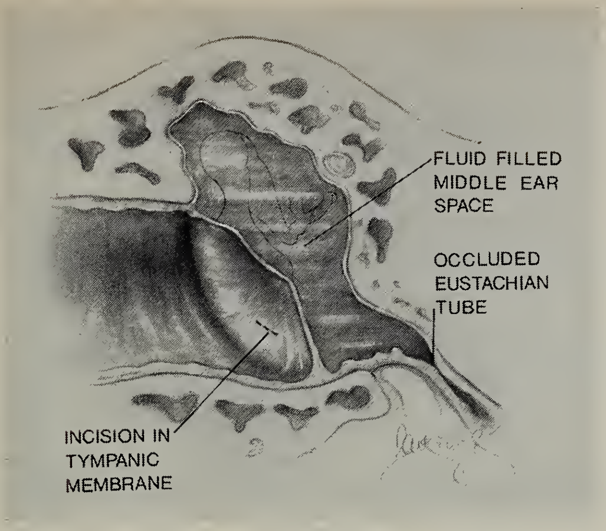

Figure 2.—Myringotomy incisions close rapidly. Prosthesis must be placed, in most instances, while etiologic factors are treated.

Surgical

Response to myringotomy and aspiration is often quite dramatic. Adults commonly experience complete relief of symptoms. Children frequently have a decidedly improved attitude toward school and an improvement in grades. In adults, the procedure is easily done in the office under local anesthesia, but for children about 14 general anesthesia is required. Since myringotomy incisions are small (Figure 2) and often heal within a few hours, a prosthetic eustachian tube is almost always placed in the site lest fluid accumulation recur and necessitate re-operation. A prosthetic tube provides prolonged middle ear ventilation while the primary etiologic factors are being treated.

The prosthetic device may be a flanged tube or one that is the shape of a collar button. It is made of polyethylene or a similar material. Generally it is left in place until it spontaneously extrudes and is found lying in the canal. This may take a few weeks to several months dependent upon several factors including the shape and composition of the device. The collar button tends to stay longer as does the shunt or mesh tube of Linthicum and House. Anterior placement of the myringotomy site also delays extrusion. In many cases it is desirable to have the prosthetic device remain in place six months or even a year, for sometimes there is otherwise a tendency to recurrence. The nature of the problem determines the kind of device to use. If the fluid is thin and there appears to be no need for prolonged ventilation, the tube is used. The button or shortened mesh tube is preferable if the fluid is tenacious and ventilation for some months is likely to be required.

Repeated myringotomy may be necessary in event of recurrence of effusion. This is not harmful. The danger to the ear and hearing is not in a properly done myringotomy but rather in failure to correct this chronic condition.

With the prosthetic device in place the patient is encouraged to place a cotton-Vaseline plug in the external meatus when showering or washing the hair lest water enter the canal and cause infection. Ear plugs are unsatisfactory for this purpose. Children are instructed not to duck their heads in the bathtub. For the same reason swimming is discouraged.

Primary Etiologic Factors

In chronic and, particularly, in recurring middle ear effusion, attention must be directed to the primary etiologic factors. Efforts to date at reconstruction of a poorly functioning eustachian tube have not been satisfactory. Several factors, however, which are correctable are known to contribute significantly to eustachian tube dysfunction. An inflammatory response, secondary to chronic adenotonsillitis, is most certainly the single greatest factor. The orifice to the eustachian tube opens directly into the adenoid area and is situated directly above the superior tonsillar pole. Chronic, purulent rhinitis and sinusitis, which frequently accompany adenotonsillitis, also result in a constant bathing of the eustachian tube orifices in purulent discharge, further aggravating inflammatory response of the tubal structures. Correctly done, removal of adenoid and tonsillar tissue almost invariably results in reduced frequency and severity of the ear disease. If there is fluid present at the time of adenotonsillectomy, myringotomy and placement of a prosthetic tube should be undertaken at the same time. This is done in hope of avoiding further operation soon afterward if the fluid doesn't clear spontaneously.

Allergy is an important etiologic factor and must be investigated when the condition does not clear after adenotonsillectomy and in adults in whom adenoid tissue is atrophic. Seldom will anti-hypersensitivity therapy clear a chronic ear problem in the presence of chronic adenotonsillitis. On the other hand, symptoms of allergic disease are commonly tolerated without development of ear disease following adenotonsillectomy. For this reason, the sequence of adenotonsillectomy for chronic adenotonsillitis followed by allergy investigation if necessary is preferable, rather than the reverse order.

Patients with recurrent ear disease must be evaluated from a general or systemic standpoint. Special attention should be given to the serum electrophoretic pattern and the blood sugar level. Any abnormal factors are, of course, treated appropriately. Gamma globulin injections are not used empirically, as some authorities believe they entail potential complications, such as the development of antibody reaction to the material. Also, such injections, in the recommended dosage, are painful and expensive. X-ray therapy to the eustachian tube is eschewed because of the reported potential of increased incidence of malignant disease in neck structures.

Since middle ear effusion may be caused by nasopharyngeal carcinoma, this possibility must always be specifically investigated.

Since excessive alcohol intake and excessive smoking can cause irritation and inflammation of the nasopharyngeal and oropharyngeael areas, patients should be warned against them.

Some physicians object to vigorous therapy of chronic ear effusion in children on the grounds that the condition often is outgrown. But sometimes spontaneous remission does not occur for several years, and sometimes continues into adulthood. In the meantime, the child is attempting to develop socially and academically in an environment of hearing loss, often to the degree that irreversible loss would require a hearing aid, or speech and auditory training or special seating in a classroom.

Finally, it must be emphasized that progressive damage may be done unless treatment is given—irreversible hearing loss secondary to an adhesive process, or cholesteatoma owing to constant, negative pressure in the middle ear space.[8] Even in cases in which repeated myringotomy is necessary, the appearance of the ear afterward does not compare with the severe deformity and derangement of the ear structures from atrophy and adhesions that are seen in untreated cases.

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BETADINE IN VAGINAL SURGERY

"Betadine has the germ-killing ability of iodine, but it doesn't have the disadvantage of causing any burning. For the past several years, I have been using full-strength Betadine solution poured right into the vagina at the operating table after the patient has had a regular preparation. I leave this soaking, an ounce of Betadine, in the vagina for about 10 minutes.

"Many men would criticize this statement and say, 'Well, you can't sterilize the vagina.' My answer to this is, 'I know you can't sterilize it, but you can certainly try.' The cleaner you get it, the more bacteria-free it is, the less chance there is of . . . serious infection. . . . If you clean the vagina and cervix out thoroughly with full-strength Betadine, I think you've done about as much as you can do toward preventing the introduction of contaminants from the vagina into the peritoneal cavity."

—James H. Beaton, M.D., Grand Rapids, Michigan
Extracted from *Audio-Digest Obstetrics and Gynecology,* Vol. 15, No. 11, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

Abortion, Gas Embolus, And Sudden Death

LESTER T. HIBBARD, M.D., *Los Angeles*

■ *In Los Angeles County, almost one-third of abortion deaths are due to gas embolus. Whenever a gas or a gas-producing liquid is injected into a pregnant uterus, a fatal gas embolus is possible because the utero-placental bed is an open avenue to the maternal circulation. The usual sequence of events is collapse, rapidly followed by death. By the time the rescue squad is summoned, the patient is either dead or beyond possibility of resuscitation.*

In the six years 1962-1967 there were 27 gas embolus deaths associated with abortion in the Los Angeles area. All the women were the victims of ignorance or indifference. Wider public knowledge of this lethal danger is the only means by which mortality can be reduced.

THE RISK OF INDUCED abortion depends on the type and severity of its complications and the quality of available medical care. Most complications respond satisfactorily to routine treatment; some require special medical skills, and a few are frequently fatal despite vigorous, expert attention.

Gas embolus ranks high among the lethal complications of abortion. Whenever a gas or frothy fluid is forced into the uterine cavity, the utero-placental bed offers an open avenue to the venous circulation returning to the heart, as well as to the cerebral circulation by way of the paravertebral veins. In this event, sufficient gas (or froth) can rapidly accumulate in the right heart and result in collapse and sudden death. By the time a rescue squad is summoned, the patient is either dead or beyond possibility of resuscitation.

The demonstration of a fatal gas embolus requires a careful autopsy technique. If the heart, vena cava and pelvic veins are opened under water, contained gas can be identified and its volume estimated. When this precaution is not observed, it is possible that significant amounts of gas will be overlooked.

In Los Angeles County, an appreciable number of maternal deaths are due to gas embolus. During the six-year period ended 31 December 1967, 27 deaths were due to gas embolus as demonstrated at autopsy. Twenty-four of the 27 deaths were associated with induced abortions. The remaining three deaths occurred at the 37th week of a normal pregnancy, ten days after curettage for an incomplete abortion, and immediately following a Rubin's tubal insufflation test inadvertently done in early

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From the District II Study Committee of the Committee on Maternal and Child Care of the California Medical Association and the California State Department of Public Health.

Presented before the Section on Obstetrics and Gynecology at the 97th Annual Meeting of the California Medical Association, San Francisco, March 23-27, 1968.

Reprint requests to: Department of Obstetrics and Gynecology, Los Angeles County-USC Medical Center, 1200 North State Street, Los Angeles 90033.

TABLE 1.—*Abortion Deaths—Los Angeles County, 1962-1967*

Maternal Deaths—No Abortion			284
Abortion Deaths			83
Infection		44	
Endotoxic Shock	29		
Peritonitis	10		
Clostridia	5		
Emboli		34	
Gas*	24		
Chemical	6		
Blood Clot	1		
Hemorrhage		5	
Miscellaneous		3	
Total Maternal Deaths			367

*Three additional gas embolus deaths were not associated with abortion.

pregnancy. These fatalities represent 29 percent of abortion deaths and 7.4 percent of the total maternal deaths during the six-year period (Table 1).

In California all maternal deaths are carefully investigated, analyzed and categorized by district study committees of the Committee on Maternal and Child Care of the California Medical Association and the California State Department of Public Health.

The material for this study is taken from the records of the District II Committee, which serves Los Angeles County. The committee bases its deliberations on a report of its own investigation plus a review of the autopsy protocol and microscope sections, when available. The most probable cause of death is recorded—irrespective of the cause of death listed on the death certificate. As a final step, the findings of the district committee are forwarded to the state committee for review.

All of the 27 women studied were either found dead, or, if witnesses were present, died rapidly despite various resuscitative measures. In all cases, the right side of the heart was filled with gas. In 18 cases autopsy reports described gas within the vena cava and pelvic veins. In addition, the cerebral vessels of four women contained air. The uteri of 24 women had unmistakable evidence of instrumentation. Another woman was postabortal, and it was known that the remaining two women had visited an abortionist.

The typical woman dying of a gas embolus was 27 years old, Caucasian, the mother of three children, and in the 15th week of pregnancy. The age range was 18 to 36 and the range of parity was zero to seven. Twenty-five of the women were in the sixth to 23rd week of pregnancy, one woman was in the 37th week of pregnancy, and one woman was ten days postcurettage for an incomplete abortion.

TABLE 2.—*Data on Abortionists in 27 Cases of Fatal Gas Embolus*

Unknown	4
Paid Abortionist	7
Friend or Acquaintance	11
Relative	1
Self	3
Physician	1
Total	27

TABLE 3.—*Scene of the Abortion in 27 Cases of Fatal Gas Embolus*

Home	16
Motel	2
Friends' Apartment	3
Abortionists' Home	4
Physician's Office	1
House of Prostitution	1
Total	27

Although motives for abortion can only be inferred, it is known that eight of the women were unmarried and six were either separated from their husbands or divorced. Only one was reported to be happily married. Of some interest is the fact that the husbands of two of the women had had vasectomy.

Identification of the abortionist and the scene of the act lend evidence to the concept that these women were the victims of ignorance or indifference (Tables 2 and 3). Few of the abortionists possessed even a modicum of skill. While the history is often incomplete, the following selected case reports illustrate several methods employed and the sequence of events which immediately preceded death.

Case. 1. During the 13th week of pregnancy, an 18-year-old college student met her boyfriend at his fraternity house. An attempt to introduce a rubber catheter into her uterus failed. Later, a plastic catheter was successfully passed, and the boyfriend blew in a large mouthful of air. The girl clutched her chest, then lapsed into unconsciousness. Mouth to mouth resuscitation and external cardiac massage failed to revive her. As was expected, the pelvic veins, vena cava and right heart were filled with air bubbles. Subsequently, the boyfriend admitted that he had learned this method of abortion from his fellow prisoners while serving time at the Sheriff's Honor Farm.

Case 2. A 33-year-old divorcee discovered herself to be 12 weeks pregnant. After two unsuccessful attempts to locate an abortionist, a friend suggested the purchase of a syringe, a catheter and a bottle of hydrogen peroxide. With the aid of the friend, the catheter was threaded into her uterus and a bulbful of hydrogen peroxide injected. Convulsions and collapse followed in rapid order. By the time the rescue squads of the police and fire departments arrived, the divorcee was dead. Her iliac veins, vena cava, and right heart contained enormous amounts of gas.

Case 3. A 24-year-old woman had twice been delivered of premature infants by cesarean section. Because of a history of one subsequent proven and several suspected spontaneous abortions, her physician undertook a fertility investigation. Not realizing that the patient was already six weeks pregnant, the physician attempted a Rubin's tubal insufflation test, using oxygen under low pressure. Within seconds, the patient murmured, "It's choking me!" Insufflation was immediately stopped—but too late. Resuscitative efforts included cardiac massage. There was gas in the pelvic veins, iliac veins, vena cava and the right heart. The uterus contained twin fetuses.

Any frothy solution can also produce a gas embolus if a sufficient amount of froth is injected into the venous circulation. The following two cases are dramatic examples of this fact:

Case 4. After $300 had exchanged hands, a 20-year-old unmarried girl was prepared for a procedure on the abortionist's kitchen table. A rubber catheter, a bulb syringe and a bottle of soap solution stood nearby. From the next room, two friends of the victim heard a swishing sound followed by a cry for help. Rushing into the kitchen, they found the girl convulsing. Resuscitation failed. Autopsy findings were: a 12-week gestation, placental separation, and a massive embolus of soap bubbles in the right heart.

Case 5. The husband of a 39-year-old mother of three young children broke open the locked bathroom door to find his wife dead on the floor. It was evident that she had been taking a douche. The coroner's autopsy showed that soapy douche water forced into the uterus had caused extensive separation of a 12-week placenta. In addition, froth filled the vena cava and right heart.

It is also possible to produce a fatal gas embolus in the postpartum or postabortal period. The following case illustrates postabortal gas embolus, and also the fact that an embolus can result from air being blown into the vagina:

Case 6. The husband of a 22-year-old mother of three children returned home ten days after she had undergone curettage for a 20-week incomplete abortion. He had been detained out of state on a burglary charge. After imbibing a considerable amount of alcoholic beverage, the couple retired for the night. In the morning, the husband awoke to find his wife dead at his side. An autopsy showed gas filling the uterine veins, the iliac veins, the vena cava, and the right heart. On questioning, the husband admitted to blowing air into the wife's vagina just before falling asleep.

As previously mentioned, gas is sometimes introduced into the cerebral circulation, presumably by way of the paravertebral veins. Evidently, this mechanism is not likely to result in death. On the other hand, it is possible that a sufficient amount of gas could produce neurologic symptoms. While final proof is lacking, the following nonfatal case might be an example of a cerebral gas embolus:

Case 7. A 21-year-old unmarried student, ten weeks pregnant, consulted an abortionist. After reaching a satisfactory agreement, the abortionist passed a catheter into her uterus. Shortly thereafter, the student "blacked out." An ambulance was summoned. On admission to a hospital, the student was comatose and all the symptoms of right hemiplegia were noted. The spinal fluid was clear. A few hours later, the products of conception passed spontaneously. During the next three days, there was continuous improvement in neurologic findings, ending in a complete recovery of function. When last seen, three years later, she was well.

Douche solutions injected into the maternal venous circulation are also capable of producing collapse followed rapidly by death, but not associated with any evidence of a gas embolus. In this event, the consistent autopsy finding is extensive pulmonary congestion and edema. Other findings are renal congestion with tubular necrosis, hemolysis, and demonstrable douche solution within the uterus and the vascular system. Death is due to acute cor pulmonale. During the period of this study, there were six deaths fitting this category.

These six women ranged in age from 25 to 42 and in parity from one to five. The periods of gestation were from seven to fourteen weeks. The douche solutions employed were soap in four cases, a substance with an odor of pine oil in one and Lysol in one. Four of the six women were dead on arrival at a hospital, one died five minutes after arrival, and one 90 minutes after arrival. The following three case histories illustrate death in such circumstances.

Case 8. For a fee of $50, two women attempted by means of a syringe and soap solution to induce abortion in a 38-year-old mother of six children. Having failed, they returned three weeks later for a second attempt. The husband, who was home sick in bed, heard a conversation in the bathroom. A few minutes later, one of the abortionists opened the bedroom door and informed the husband that he was wanted. He found his wife dead on the bathroom floor in a puddle of soapy water. An autopsy showed a 14-week fetus, acute pulmonary congestion and edema, and extensive intravascular agglutination and hemolysis.

Case 9. A 31-year-old divorcee, the mother of an 11-year-old son, had accomplished several previous abortions. On this occasion, the order of events was as follows: 3:30 a.m., found lying on the bathroom floor, was helped to bed; 6:00 a.m., collapsed while being helped to an automobile by her landlady; 6:15 a.m., pronounced dead by an ambulance crew. The uterus contained a 14-week fetus as well as soap solution. There was more soapy material in the lungs and the heart, but no air embolus. In addition, there was pronounced pulmonary congestion, edema, coagulation, and fibrin deposition in the pulmonary veins.

Case 10. A 35-year-old woman was living with her four children and common law husband. She had previously been unsuccessful in aborting a seven-week pregnancy by means of turpentine and castor oil. At 10:30 p.m., she awakened her husband, telling him that she had fainted in the bathroom. She was coughing up pink froth. At 12:40 a.m., she was admitted to a hospital, alive but in extreme respiratory distress. Five minutes later she was dead. Her uterus had an odor of chemical disinfectant as well as evidence of instrumentation. Her lungs were filled with edema fluid and there was fluid in the pericardial sac. Later, a bottle of Lysol and a syringe were found in her bathroom.

Discussion

In metropolitan areas such as Los Angeles County, induced abortion is the leading cause of maternal death. While the majority of deaths are due to the complications of infection, a substantial proportion (29 percent in the present series) are the direct result of a gas embolus. Death due to gas embolus is typically sudden, occurring shortly after the injection of either a gas (or a liquid capable of producing gas) into the uterine cavity. Because the utero-placental bed is an open avenue to the maternal circulation, a lethal quantity of gas can easily accumulate in the right heart. By the time resuscitation is started, the patient is either dying or dead.

Other induced abortion deaths can also be directly or indirectly attributed to the injection of various toxic solutions. Soap solution, in particular, is capable of producing fibrin deposition in the pulmonary circulation sufficient to result in pulmonary congestion, pulmonary edema, and death due to an acute cor pulmonale. If the patient does not die immediately, she may die later of renal complications or as the result of infection. If the latter, it is probable that infection gained a foothold through uterus tissue damaged by the solution.

The technique of induced abortion by means of a syringe and a catheter stiffened with a coat-hanger is common knowledge among the women of California. What they do not fully realize is the danger of this act. Since, in many cases, even the finest of medical care will not avail, it is clear that there should be a more vigorous attempt to educate the public to the possible consequences of this hazardous procedure.

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Chemical Pollution From Transportation Vehicles

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■ *Recent publicity on electrically powered vehicles notwithstanding, the gasoline engine will probably be the principal power plant for passenger cars for at least the next decade. Chemical pollutants discharged by the gasoline engine are now under partial control. Motor cars of 1968 and 1969 model discharge only about 30 percent as much carbon monoxide and unburned hydrocarbons as do older models. In theory, carbon monoxide, unburned hydrocarbons and oxides of nitrogen ultimately can be completely removed from gasoline engine exhaust. In order to accomplish this it would be necessary to modify cars to operate satisfactorily on a lean mixture and perhaps to use a catalyst in the exhaust system.*

Present designs of gas turbines for aircraft and for future projected application to ground vehicles yield pollutants (except for smoke) at levels below those of gasoline engines for a decade to come. It has also been shown possible to eliminate smoke as well as odor from the gas turbine. Thus with proper effort it is feasible to reduce pollution of the atmosphere due to transportation to an acceptable level, even if electrically or alternatively powered vehicles cannot be developed for a decade.

SIXTY PERCENT OF atmospheric pollution in the United States results from transport of people and goods. Substantially all of this 60 percent is from gasoline powered motor vehicles. Minor but highly visible and annoying contributions are made by trucks, buses and jet aircraft. Hence the passenger automobile is a prime target for attempts at alleviation of air pollution.

Pollutants are principally of two kinds: those which can be seen, usually as smoke, and those which are invisible, such as carbon monoxide, unburned hydrocarbons, carbon dioxide, and oxides of nitrogen and sulfur. Even water vapor can be considered a pollutant under certain conditions, but will not be so classified here.

Timely and most pertinent is the recent government publication, "The Automobile and Air Pollution: A Program for Progress," by Richard S.

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Portions of the work reported herein supported by U.S. Public Health Service Grant AP-385-02.

Presented as part of a round table on Motor Vehicle Pollution Control at the Environmental Health Conference presented at the 97th Annual Session of the California Medical Association, San Francisco, March 23 to 27, 1968.

Reprint requests to: Thermal Systems Division, Division of Mechanical Engineering, University of California, Berkeley 94720.

TABLE 1.—*Relative Emission Contribution on Average Trip by Average Automobile Not Equipped for Reduction of Emissions**

	Percent		Hydrocarbons		Carbon Monoxide		Nitrogen Oxides	
Mode	Time	Sample Volume	Concentration ppm	Contrib. %	Concentration %	Contrib. %	Concentration ppm	Contrib. %
Idle	15.0	4.2	750	4.4	5.2	5.0	30	(0.05)
Cruise	16.0	16.8	300	7.0	0.8	3.1	1500	10.6
Accelerating	36.7	69.9	400	38.5	5.2	83.1	3000	89.3
Decelerating	32.3	9.1	4000	50.1	4.2	8.8	60	0.1

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*These data were collected under conditions determined to be average during the average normal urban trip ten years ago. They form the base for criteria established first for control of vehicular emissions in California (in 1966) and now for the whole United States (in 1969).

Morse of Massachusetts Institute of Technology. This document results from a study by the Panel on Electrically Powered Vehicles, reporting to the U.S. Department of Commerce. It is a thoroughgoing assessment of the air pollution problem in the United States, of progress being made to alleviate pollution and of the prospects for methods for vehicular propulsion other than by reciprocating engines. A blue ribbon collection of 40 scientists and engineers, equally representative of industry, government and academe, was involved in the study, conclusions, and recommendations. The report in part states, most significantly:

- "Emissions from automotive vehicles are largely responsible for the formulation of photochemical smog in Los Angeles and some other areas, and vehicles are the principal source of carbon monoxide in the atmosphere.
- "During the next decade, in the normal course of events, no significant reduction in total air pollution will be achieved through the introduction of unconventional low-polluting vehicles into the current population of approximately 90 million vehicles. The state of technology does not permit the current development of an economically feasible electric car except for special-purpose, limited-range use."

These two very important statements taken together establish the base and framework for this presentation, which will deal with the causes of undesirable chemical emissions from engines, the progress being made to reduce them and the expectation for ultimate accomplishment in light of present knowledge. Consideration was not limited to passenger cars, trucks and buses. Pollution generated by aircraft, railroad engines and ships was also taken into account although they do relatively little polluting of the air.

Atmospheric Pollution from Motor Vehicles

Almost 99 percent of the approximately 90 million combustion engine powered vehicles on the roads and highways of the United States today use gasoline. Of the 1 percent remaining, a relatively few use butane and propane. Most of this 1 percent is diesel powered. Approximately 75 billion gallons of fuel per year are now being burned in these 90 million vehicles. Projections indicate an increase in the next decade of about 50 percent in this fuel consumption.

By comparison, present use of fuels by domestic air transport carriers is about 5 billion gallons per year. Indications are that this figure will rise to 20 billion gallons a year by 1977, almost all of it for jet aircraft.

Direct comparison cannot be made between ground vehicle and air transport fuel consumption rates in talking about air pollution, for only approximately 1 percent of the total amount of fuel consumed by aircraft is burned close enough to the ground to pollute the air we breathe. This small amount, however, is very obvious by its odor and visibility in the vicinity of airports.

Passenger Car Emissions

Carbon monoxide is by itself a poisonous gas. Unburned hydrocarbons of certain aromatic composition (benzopyrene and benzanthracene as examples) are carcinogens. Oxides of nitrogen are suspected of relationship to emphysema, although there is not full agreement on this point. Other hydrocarbons when combined with oxides of nitrogen in the air, particularly under ultraviolet irradiation, cause murk, irritate eyes and interfere with respiratory functions. The relative amounts of each of the primary contributing materials which are produced on an average urban trip by an average automobile not equipped for reduction of emissions are shown in Table 1.

By extension, the emissions per vehicle as indicated in Table 1 can be used to estimate the total pollutant contribution which automobiles are at

TABLE 2.—*Estimate of Amounts of Pollutants Discharged Annually by Motor Vehicles in the United States*

Pollutant	*Tons per Year*
Carbon Monoxide	66,000,000
Oxides of Nitrogen	6,000,000
Hydrocarbons	12,000,000
Sulfur Oxides	1,000,000
Lead Compounds as lead	190,000
Particulates	1,000,000

TABLE 3.—*Total 1966 Air Pollution in the United States from Various Sources*

Source	*Tons per Year*	*Percent of Total*
Refuse Disposal	5,000,000	3.5
Space Heating	8,000,000	5.6
Power Plants	20,000,000	14.1
Industry	23,000,000	16.2
Motor Vehicles	86,000,000	60.6

present making to the atmosphere in this country (Table 2).

The total contributed by automobiles is measured against the amounts contributed by various other sources in Table 3.

Control of Vehicle Emissions

Obviously, some radical corrective measures had to be taken, and they were. The law now prescribes that new gasoline powered vehicles must be so equipped in this country that carbon monoxide on the average shall not exceed 1.5 percent, down by 60 percent from uncontrolled levels. Unburned hydrocarbons are not to exceed an average of 275 parts per million, a reduction of about 70 percent. No general control is yet being applied to the other materials.

Time Factors in Control of Pollution by Motor Vehicles

The application of these new controls will have a gradual effect on the general level of air pollution attributable to motor vehicles. The reason is implicit in Chart 1, which illustrates the rate at which vehicles now in operation are retired and are replaced by new ones. Note that it will require almost five years for half of the motor vehicles in operation to be so equipped, assuming that only new cars will be supplied with emission control systems. The prospect for application of similar controls to used vehicles appears completely negative, even for California, where the problems of air pollution are particularly severe. In the interim, moreover, it is expected that the number of motor vehicles will increase. This growth rate averaged three million vehicles per year over the last two decades. A projection of these factors to such metropolitan centers as Los Angeles, indicates that air pollution from motor vehicles will depart from its previous increasing trend, but that the level in the next decade, and beyond, will still be above that considered desirable or even tolerable. A typical projection for the Los Angeles metropolitan area is illustrated by Chart 2.

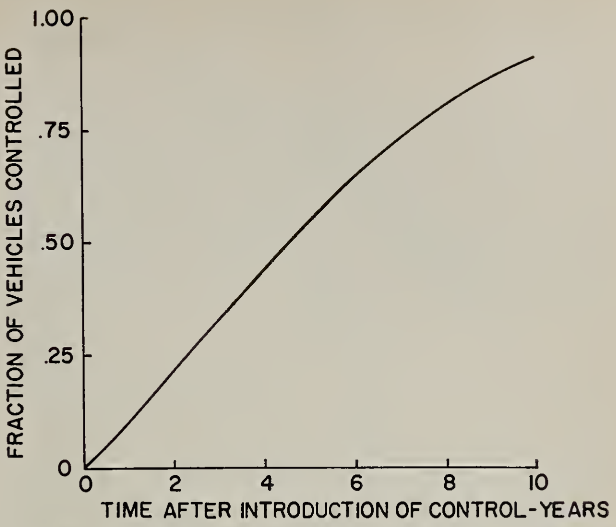

Chart 1.—Influence of survival of uncontrolled vehicles and replacement with controlled vehicles.

Demonstrated and Theoretical Limits To Gasoline Engine Emissions

Even under the conditions of ultimately sucessful control to levels indicated in the previous para-

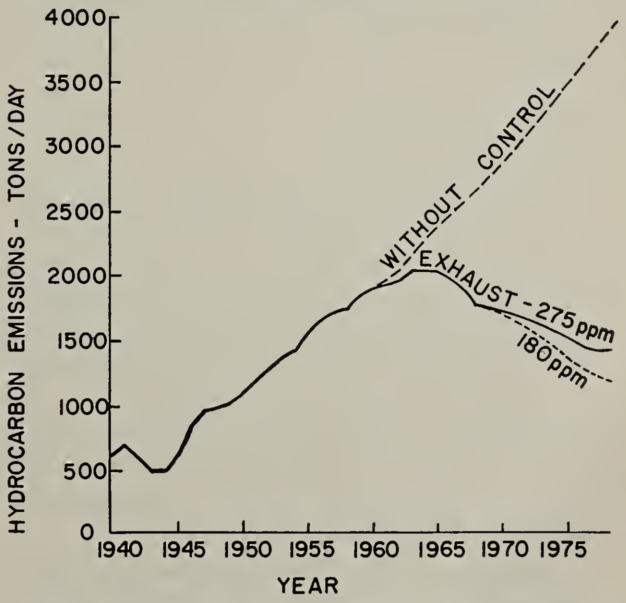

Chart 2.—Hydrocarbon emissions for motor vehicles in Los Angeles County.

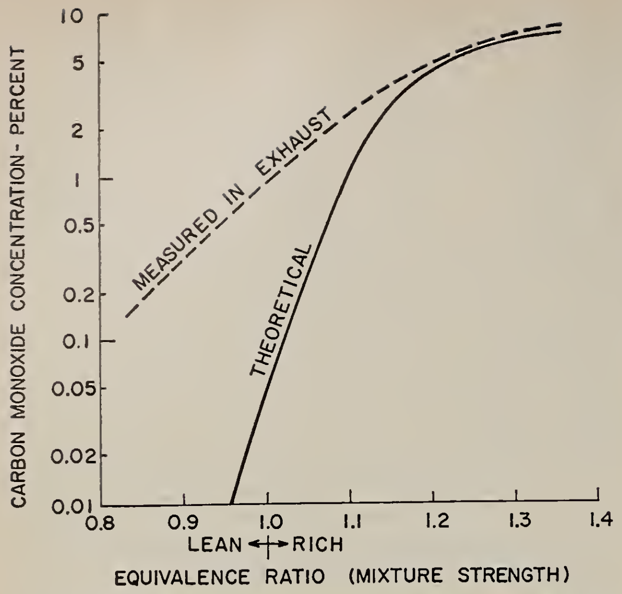

Chart 3.—Carbon monoxide from a gasoline engine.

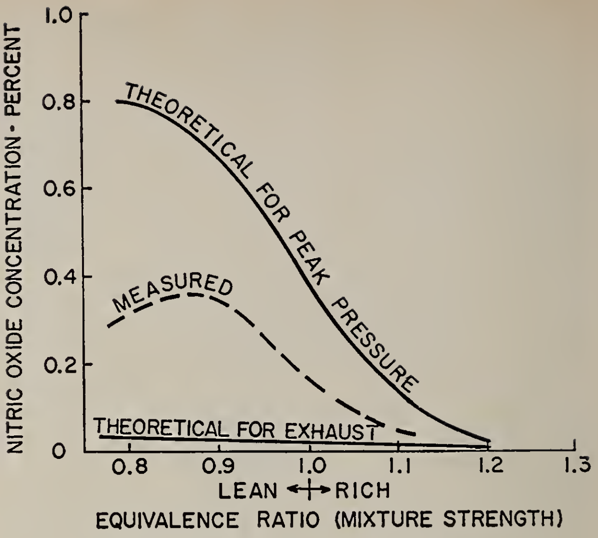

Chart 4.—Nitric oxide from a gasoline engine.

graph, motor vehicles will still be polluting the atmosphere. One view would have as an ultimate goal a reduction to almost zero of all noxious materials. The question is then one of determining if existing piston engines can be modified to produce zero emissions. Deciding if it is theoretically possible to do so entails making use of a knowledge of chemical and combustion factors. The three products of combustion which appear to be of the most pressing present concern will be considered carbon monoxide, hydrocarbons and oxides of nitrogen. The others, sulfur oxides and lead, can be controlled through elimination of them from the fuel, a costly and controversial prospect.

Demonstrated Levels of Vehicle Emission Control

Carbon Monoxide — The chemical principles which govern the generation of carbon monoxide are well known. Generally, any mixture which contains more fuel than the oxygen available to burn it completely will disproportionately produce carbon monoxide. Automobile engines developed up to the last few years, before air pollution was recognized as a real problem, tended to operate best at fuel rich mixture ratios. That is why the levels of carbon monoxide from uncontrolled vehicles was 3.5 percent.

The principal way that carbon monoxide has been successfully decreased to 1.5 percent in 1968 model engines is through leaner mixtures for carburetion, particularly at idle conditions and at slow vehicle speeds. This 1.5 percent level is considered still too high. The question then is one of the extent to which leaning of the mixture can further reduce emission of carbon monoxide.

Chart 3 illustrates the theoretical and actually measured levels of carbon monoxide which obtain in a typical gasoline engine exhaust. Very lean mixtures would be required to reduce levels to 0.5 percent or less. This 0.5 percent is the level which is indicated as being commercially feasible of attainment in the next decade. At the moment there is little evidence that levels very much less than 0.3 percent can be obtained inherently from gasoline engines as they are now constructed or as they are projected for a decade or more.

Unburned Hydrocarbons—The source of unburned hydrocarbons from well regulated engines is generally conceded to be a consequence of flame quenching at the wall and in the interstices of the combustion chamber. Factors which determine just how much fuel will be in that quench area include completeness of evaporation, mixture ratio and compression ratio. Better carburetion, leaner mixture ratios and lower compression ratios all contribute to lowering levels of unburned hydrocarbons. Present indications are that hydrocarbon discharge from gasoline engines can be reduced to a level of 50 parts per million in the next ten years. This is still greater however than some environments are considered capable of assimilating from large concentrations of traffic.

Oxides of Nitrogen—Chemically speaking, oxides of nitrogen can be treated in the same manner

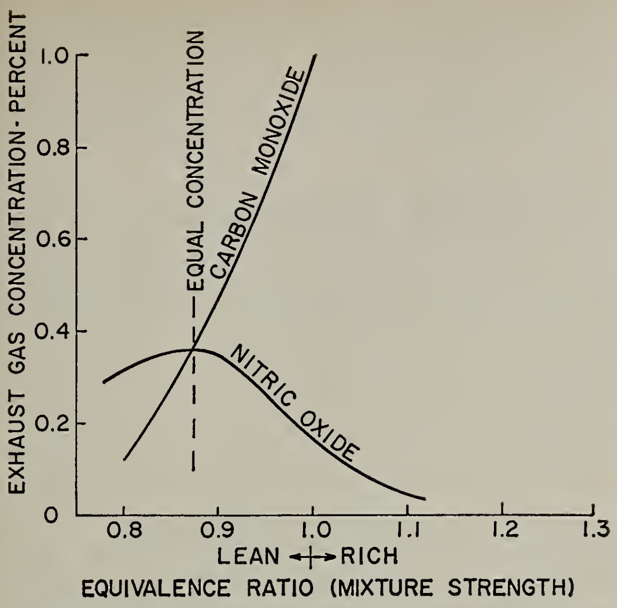

Chart 5.—Comparative carbon monoxide and nitric oxide from a gasoline engine.

as carbon monoxide. The amounts to be expected can be calculated from a knowledge of the temperatures and pressure in the combustion process. It evolves that nitric oxide (NO) is the oxide of nitrogen which is actually formed in the engine. Chart 4 shows the results of such calculations and the measured concentrations.

It can be noted that the oxides of nitrogen exceed the levels to be expected in the exhaust by a considerable factor. This is a consequence of a "quench" mechanism which fixes the nitric oxide once it is formed in the combustion process.

Charts 3 and 4 show that the very fuel-air ratio factors which tend to reduce the concentration of carbon monoxide result in an opposite effect for nitric oxide. Thus there is a problem associated with an attempt at concomitant reduction in quantities of both.

Present levels of oxides of nitrogen in gasoline engine exhaust are about 1,500 parts per million (0.15 percent). Considerable evidence is available to show that oxides of nitrogen in the atmosphere *per se* are harmful, both to plants and to animals, including humans. Thus it can be expected that this pollutant will also be a candidate for reduction as a component of engine exhaust.

Some methods for reduction are already available—for example, the recycling of engine exhaust. The method is simple and successful. Reduction in oxides of nitrogen is attributed to the lowering of combustion temperatures. It is expected that this method, or others which are under study, might be invoked in the near future to reduce exhaust content of nitric oxide to a level of 250 parts per million.

Thus, the gasoline engine appears to be inherently capable of greater control of these three principal pollutants than is being exercised at present, and even may be controlled to levels which, for now, might be acceptable. Beyond this, the means for further reduction do not appear either clear or easy.

Theoretical Lower Limits For Vehicle Emissions

It appears that for substantially complete elimination of carbon monoxide, unburned hydrocarbons and nitric oxide from the exhaust, external means will be needed rather than internal modifications to the engine. A theoretical view can be taken of the potential for reducing emissions to a very few parts per million. One such possible method would make use of the observation that equal amounts of carbon monoxide and nitric oxide will be exhausted from a given engine under lean mixture operating conditions. Chart 5, a composite of Charts 3 and 4, illustrates this "match" point.

It shows that carbon monoxide and nitric oxide levels on the order of 0.35 percent are equally produced by this particular engine when operating on a mixture ratio that is approximately 13 percent lean. There are such "match" points in all engines, although not necessarily at this same condition.

One proposal that has been made is to make use of this observation to bring about a simple exchange of oxygen between these two undesirable components in a reaction — $2NO + 2CO \rightarrow N_2 + 2CO_2$ — which produces a minimally undesirable product of combustion.

Three major developments must take place before such a proposal could be effected:

1. Engines must be made to operate satisfactorily at the mixture ratios which will produce the "match" point. This is considerably leaner than is the case at present, but is a technical feasibility.

2. Extremely close control will have to be exercised over fuel:air mixture ratios. This level of control may not be possible with carburetors as they are now known and thus may involve a new configuration of fuel supply.

3. A catalyst will be required to hasten the oxygen exchange reaction between carbon monoxide and nitric oxide. Unless hastened, this reaction is too slow.

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The problem of limiting unburned hydrocarbons from gasoline engines to almost zero concentration is a matter of providing sufficient oxygen, an appropriately high temperature and good mixing. If gasoline engines can be developed which will operate at the lean mixture ratios which produce equal quantities of carbon monoxide and nitric oxide, the oxygen necessary for conversion of unburned hydrocarbon is already available in the exhaust. An adiabatic mixing chamber* at the exit from the engine, again perhaps with a catalyst to hasten the reaction, should provide the possibility for reducing the concentration of hydrocarbon to at most a very few parts per million.

Nature and Concentration Of Gas Turbine Emissions

It will not be long before the gas turbine is the only powerplant used for commercial aircraft. It is also under serious consideration for ground vehicles. Hence emissions from turbines are a matter of concern. Limited but dependable data show that pollutant concentrations exhausted from turbine engines are below those that can be reached by gasoline engines either now or in the next decade. When data are adjusted to make a fair comparison, it is shown that automotive turbines as now designed produce no more than 0.3 percent carbon monoxide, less than 100 parts per million of hydrocarbon and (with one particular exception) less than 350 parts per million of oxides of nitrogen.

Concentrations produced by aircraft turbines are similar to those of the automotive but that which is emitted to the atmosphere is quite obvious from the odor and smoke around metropolitan airports. The reasons for this smoke and odor are known. The present jet engines are all developments from military design in which criteria for combustion chambers are principally associated with maximum high altitude performance stability. Such criteria are not necessarily compatible with minimal smell and smoke at sea level, or while idling, or taxiing, or taking off. Design and development of future jet engines for civilian aircraft take this factor into account, with the prospect that the engines used for civilian air transport can be virtually free of both odor and smoke.

Neither smoke nor odor is detectable in the exhaust of recently designed automotive turbines. Assuming therefore that manufacturing cost could be reduced to a reasonable level, a widespread conversion to this form of powerplant might be a solution to the near future problems of passenger car, truck and bus emissions.

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*An adiabatic mixing chamber is a modified exhaust manifold which is maintained at higher temperatures and which perhaps could contain a catalyst. Such devices have been demonstrated to be practical. Questions of increased cost to the vehicle owner have not yet been fully explored. However, some systems already tested would appear to be free of maintenance problems.

PENETRATING WOUNDS OF THE NECK

"Most surgeons tend to prefer exploring routinely penetrating wounds of the neck, such as gunshot and stab wounds. But is this always feasible? We'd like to divide the neck into three zones [and consider the value of angiography in each]. Injuries below the clavicle may involve the lungs or the great vessels. For these injuries, angiography is helpful, not only in diagnosis, but also in deciding on the surgical approach. In the midneck, where we have esophagus and trachea as well as the carotid and jugular vessels, the role of angiography is perhaps less important, since routine exploration through an anterior sternocleidomastoid muscle incision is usually adequate for these structures. However, above the mandible, exploration without angiographic control may be something of a nightmare."

—ROBERT J. FREEARK, M.D., Chicago
Extracted from *Audio-Digest Surgery,* Vol. 15, No. 21, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

School Health-History Forms

A Study of Those Used in California, with Suggestions for Changes

GABRIEL SMILKSTEIN, M.D., *Claremont*

■ *The health history form has an important role in the evaluation of student performance. Recommendations for therapeutic programs may be based on information gained from the health history.*

One hundred three California high schools reported the frequency of their use of the health history form. Only 56 percent of these schools require health histories of their new students. Only 38 percent obtain health histories from their athletes.

Sixty-four of the 103 California high schools responding enclosed copies of the health history form in use in their schools. Analysis of these forms revealed a lack of uniformity of content and, in general, failure to obtain information pertinent to the in-school student problem.

A format for a school health history form whose primary purpose is to reveal school-related health data was developed.

THE HEALTH HISTORY has been established as an essential part of the school age child's health appraisal. Its purpose is to give information on the genetic and environmental factors in the student's past medical history which might influence his education. The information gained from the student and his parents in the health history may serve the school to understand a student's performance or to detect a problem which might be subject to corrective measures.[2]

The purpose of this paper is to analyze the effectiveness of the health history as reflected in a response to a questionnaire sent to California high school administrators.

One hundred three responses were received from 200 questionnaires that had been sent to California high schools which were representative on the basis of school size and geographical locations. In the period covered by the study (1967-68) there were 856 high schools in the state. Questionnaire replies and copies of the health history forms used by the respondents were received from the three major city school systems of San Diego, Los Angeles and San Francisco, as well as from representative high schools throughout the state.

The replies to the questionnaire from the 103 California high schools are tabulated in Table 1. In this study only 56 percent of the schools indicated that their new students are required to complete health history forms. K. D. Rogers, in his "Review of the Health Appraisal of the School Aged Child," indicated that the health history is the most neglected yet most important aspect of the analysis of student health problems.[4] From the health history the school official could obtain

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Submitted 30 July 1968.

Reprint requests to: 335 Yale Avenue, Claremont 91711.

information not available by direct examination, teacher observation, or usual school screening tests.[5] It is also the most economical method for the school to obtain health information.

There is a tendency to overemphasize the in-school physical examination of the school child. The effectiveness of the annual in-school physical examination as a case-finding procedure for serious diseases has been studied and found wanting.[1,4] The conditions which have been discovered on in-school physical examination and which may be improved or corrected by health care are almost all in the categories of vision, hearing, dentistry, nutrition, and skin.[3] It is from the health history that the essential information on residual defects from serious diseases or injuries must be obtained.[5]

Sixty-four of the 103 respondents in this study enclosed a copy of their health history form. The items in the 64 health history forms were listed and the frequency of their appearance on the forms is summarized in Table 2.

The forms were characterized by a lack of uniformity of content. It would also appear that in general there was a failure to obtain information pertinent to the in-school student problems.

Questions on family history, which could contribute important genetic and environmental information, were included in only 14 (23 percent) of the forms. Questions on mental or emotional health appeared in 11 (17 percent). The answers in this area of inquiry varied from the superficial "difficulty in concentration" to a more forthright "desires psychiatric help."

Only 39 (38 percent) of the 103 schools which responded offered a health history for athletes. It would appear that at a time when all those involved in sports medicine are increasingly concerned with

TABLE 1.—*Summary of 103 Responses to Questionnaire Sent to 200 High Schools in California*

	(Total 103)
All students complete a health questionnaire	47
Upon entering high school	45
As freshmen	32
As new students	58
Beginning of each academic year	13
All athletes complete a health questionnaire	39
Beginning each academic year	29
Beginning each sports session	36

Additional comments:
Medical examination required for participation in athletic program.
Medical examination recommended for incoming ninth graders.
Health questionnaire not required since there is a rather complete medical information card and packet from the feeder junior high schools in the area and on all entering students.
Physical examination given by school physician/given by student's family physician.
Examination given routinely upon entrance by M.D. and R.N.
Examination at the beginning of sports season when the student has sustained an injury in a preceding sport.
Athletes must complete C.I.F.P.F. Doctor's Card.
Personal interview by school nurse instead of questionnaire.

TABLE 2.—*Summary of Major Items on Health History Form From 64 California High Schools*

	Items Asked About	*Schools* *No.*	*%*
Head	Headaches	31	48
	Head injury	15	23
	Dizziness or fainting	39	61
Eyes	Glasses or contact lenses	32	50
	Eye defects	34	53
Ear, Nose, Throat	Hearing defects	33	52
	Punctured ears	2	3
	Recurrent ear infection, "discharging ear"	16	25
	Broken nose	1	2
	Speech difficulties	9	14
	Sinusitis	6	9
	Dental problems	28	44
Neck	Neck injury	2	3
	Thyroid problems	4	6
Heart and Lungs	Tuberculosis or contact	49	77
	Heart disorder	46	72
	Asthma	36	56
	Symptoms of lung disease	28	44
Abdomen and Genito-Urinary	Abdominal symptoms	18	28
	Hernia	52	81
	Loss or absence of testicle	1	2
	Loss or malfunction of one kidney	11	17
	Kidney disease	11	17
	Enuresis or bedwetting	10	16
Bone and Joint	Ankle injury	1	2
	Knee injuries	7	11
	Joint disability	26	41
	Bone disease	6	9
	Back trouble	12	19
Nervous System	Poliomyelitis	33	52
	Convulsion or epilepsy	37	58
Endocrine, Blood or Tissue Diseases	Diabetes	39	61
	Skin infection	15	23
	Rheumatic fever	47	73
	Weight change	3	7
Present Use of Medications	Specific medications	10	16
Emotional or Mental History		16	26
Immunization	Tetanus	52	81
	Polio	49	77
	Tbc skin test or x-ray	32	50
Allergies	Bee stings	5	8
	Food	4	7
	Medicine	4	7
	Hay fever	22	34
	Allergies	27	42
Indicate If You Have Had	Operations	45	70
	T&A	11	17
	Appendectomy	8	13
	Accidents	31	48
	Serious illnesses	50	78
Health Habits	Use of:		
	Alcohol	1	2
	Tobacco	2	3
	Stimulants	1	2
	Sedatives	1	2
Do You Have Any Health Problems		4	6
Infectious Diseases (17 diseases listed)			

the prevention of injuries, the role of the health history is being neglected. A review of Table 2 will show that most forms are deficient in information which would be of real value to the team physician, the coach, or the trainer. Fewer than 5 percent of the 64 schools whose health history forms were studied had items on punctured ear drums, broken nose, neck injury, loss of function or absence of testicle, or loss of function or absence of kidney. These deficiencies could be critical in the evaluation of the athlete.

Not one health history form received had an item on the time of onset of menses or inquiry as to dysmenorrhea. The time of onset of menses can give valuable information on student maturation age. Dysmenorrhea is a major cause of absenteeism for high school girls. Identification of students with recurrent dysmenorrhea would allow the school nurse the opportunity to counsel these students about their problem.

An ideal health history form should offer a review of the student's physical and emotional system. The items in this review should have application in the school setting. It would appear that most health history forms now in use follow the classical design of those used in a physician's office. Hence they contain much information which is of little use to the educator. An example of items appearing on the health history forms which would be irrelevant to the educator are questions on trachoma, enlarged nodular thyroid, rectal bleeding, kidney stones, lax rings, tumors, and malaria.

Appendix A shows a health history form that

APPENDIX A—*Suggested Health History Form Developed to Overcome Shortcomings of Forms Now in Use*

Name	Age
Address	Grade
Phone	Family Doctor
Date	Family Dentist

Family History: Yes No
Does anyone in your immediate family have:
Diabetes
Allergies (Asthma, Hives, Hay fever)
Migraine
Tuberculosis
Emotional Illness

Medical History: Yes No
Have you had or do you now have any of the following:

Head
Brain concussion
Tendency to lose consciousness or faint
Recurrent headaches
Skull fracture
Convulsions or epilepsy

Eyes
Uncorrectable vision in one eye
Blindness in one eye
Eye injury
Glasses or contact lenses

Ear, Nose, Throat, or Mouth
Hearing loss
Perforated ear drum
Recurrent discharge from an ear
Recurrent sinus infection
Broken nose
Repair of a broken tooth
Dental plate
Orthodontia
Difficulty with speech

Neck
Neck injury

Heart and Lungs
Asthma
Heart disease
Rheumatic fever
High blood pressure
Recurrent or persistent cough

Abdomen and Genito-Urinary
Hernia
Loss of function or absence of a kidney
Boys: Loss of function or absence of a testicle
Girls: Age of onset of menses ....
Marked discomfort with menstruation

Bone and Joint
Back injury or recurrent backache
Knee injury
Ankle injury
Shoulder injury
Other joint disability
Bone infection
Bone fracture
Osgood-Schlatter's disease

Endocrine, Blood
Diabetes
Bleeding tendency or bruise easily
Anemia

Skin
Recurrent rash
Fungus infection
Athlete's foot
Recurrent boils

Allergies
Asthma
Hay fever
Hives or rash
Bee sting reactions
Medicines
(If yes, name) ....

Medications
Routine med.: Is there a medicine you take on a regular basis?
If yes, name ....
Emergency med.: Is there a medicine you take for emergency use?
If yes, name ....

Emotional or Mental
Would you wish to discuss an emotional problem or treatment program with a school nurse or psychologist?

Immunization	Dates last booster
Tetanus-diptheria	......
Polio	......
Smallpox	......
Measles	......

includes the items which would be pertinent to the needs of school officials. Information is not asked on past operations and illnesses which would be found on the health history form in a physician's office, for it would contribute little to the school child's health history unless accompanied by a record of residual defects. The physical and emotional system review gives a health profile which is aimed to reveal these residual defects.

It is suggested that the school nurse screen the health history form. In large school districts, or for purposes of data collection, these forms could be prepared for machine processing. The school nurse or a responsible member of the school health department should then see that pertinent information is transmitted through appropriate channels. Teachers, department heads, guidance teachers, school psychologists, coaches and the like should receive reports on students whose health history form suggests problems in their respective departments.

This study would suggest that the health history form as it is used in the California high schools is at times archaic, inconsistent and poorly designed for the evaluation of student health problems. It would appear desirable that school health officials and educators take steps to review, update, and standardize the health history form in the schools of the State of California.

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FACTORS IN DECIDING UPON RENAL TRANSPLANT

"In a patient who has renal failure, how does one decide whether to use maintenance chronic hemodialysis or to submit the patient for renal transplantation?

"The guidelines which govern this decision are in the earliest formative stage. I think the results with well-matched siblings are so good now that if you have a patient who has a group of siblings, this probably is a reasonable thing to do right at the outset. On the other side of the coin, the patients who seem to be doing the best on dialysis are patients in the older age group, above 35. The older they are, the better they seem to do. Our earlier fears about older people not being able to handle dialysis physically are being dispelled. On the other hand, the young, active people—particularly young males—have a very difficult time adjusting to the restraints of dialysis; from that side of the picture, that's the kind of patient I think should be transplanted straight away. Children are not growing well on dialysis, if at all."

—BELDING H. SCRIBNER, M.D., Seattle

Extracted from *Audio-Digest Internal Medicine,* Vol. 15, No. 21, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

CASE REPORTS

Intramural Hematoma Of the Duodenum

LOUIS ADLER, M.D., AND
H. JEROME STULBERG, M.D., *Los Angeles*

INJURY TO THE abdominal organs by impact with a blunt object accounts for only about one of every 1,260 hospital admissions due to trauma.[1] The organs most frequently involved are the liver, spleen and kidneys; less frequent, the stomach, small bowel and colon. Localized intramural hematomas of the duodenum are a rare phenomenon, fewer than 60 cases having been recorded in the world literature.[2] In the following case the radiographic findings were characteristic of this entity, and in retrospect a corroborating clinical history was obtained.

Report of a Case

A seven-year-old boy was admitted to the hospital with a history of diffuse abdominal pain, nausea and vomiting for 24 hours. The vomitus was clear and occasionally projectile in nature. As a 200 mg chlorpromazine suppository had been given shortly before he entered the hospital, the patient was unable to give a satisfactory history.

On examination he was observed to be minimally dehydrated and very lethargic. Diffuse abdominal tenderness was noted but there was no rebound tenderness or rigidity. The day following admission the hemoglobin and hematocrit were noted to have dropped to 9.3 gm per 100 ml and 28 percent from admission levels of 12.5 gm and 36 percent. Serum amylase at this time was elevated to 463 units. Roentgen examination of the abdomen, which had shown no abnormality on admission, now revealed an ill-defined soft tissue mass in the left upper quadrant of the abdomen, producing extrinsic pressure on the greater curvature aspect of the stomach and inferior displacement of the transverse colon (Figure 1).

A barium meal study later that day showed almost complete obstruction of the second portion of the duodenum by an intraluminal mass (Figure 2). The mass extended from the second portion of the duodenum into the proximal jejunum, and in a few areas a "coiled spring" appearance of the involved bowel was seen (Figure 3). A diagnosis of intramural hematoma of the dedenum extending into the jejunum was made and the child was prepared for operation. By this time he was alert enough to give a history and it was learned that he had fallen and struck his abdomen on the end of a cane 48 hours before admission to the hospital.

At operation a subserosal hematoma of the duodenum (Figure 4) extending from the region of the ampulla of Vater to a point 10 cm distal to the ligament of Treitz was found, and the contents were evacuated by incising the serosa. The proximal portion of the hematoma was seen to be

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From the Department of Diagnostic Radiology, Cedars-Sinai Medical Center, Cedars of Lebanon Hospital Division, Los Angeles.

Submitted 8 August 1968.

Reprint requests to: Department of Diagnostic Radiology, Cedars of Lebanon Hospital, 4833 Fountain Avenue, Los Angeles 90029 (Dr. Stulberg).

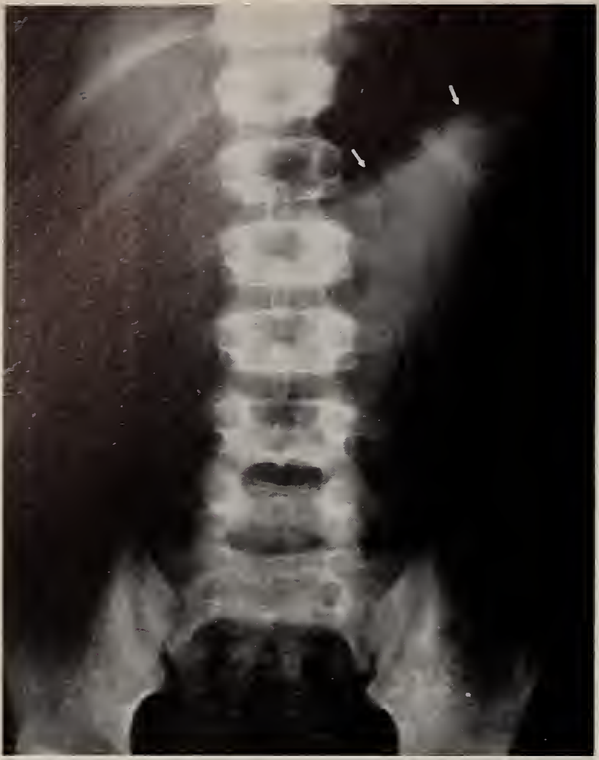

Figure 1. — Film of the abdomen with patient supine demonstrates an ill defined mass producing extrinsic pressure on greater aspect curvature of stomach (upper arrows), and causing inferior displacement of transverse colon (lower arrow).

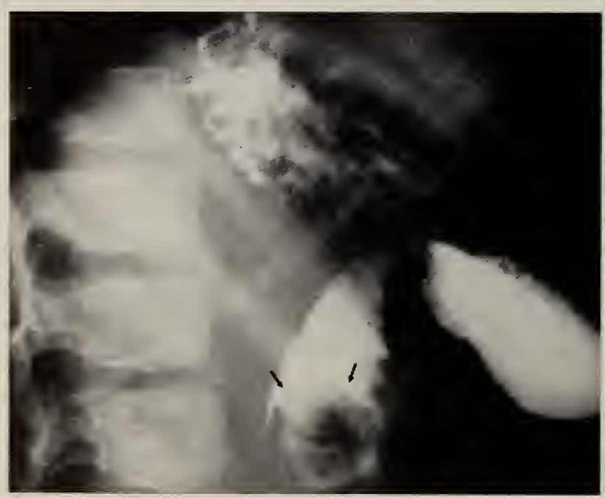

Figure 2.—Barium meal study showing almost complete obstruction of second portion of the duodenum by an intraluminal mass.

impinging upon the main pancreatic duct, causing partial obstruction, which accounted for the elevation of serum amylase. The body of the pancreas was soft and pliable, but the head of the organ was firmer than normal, suggesting traumatic pancreatitis. The remainder of the viscera were normal. The child recovered promptly.

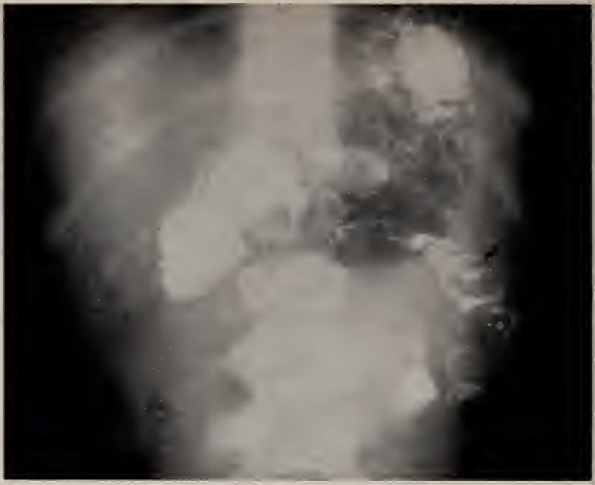

Figure 3.—"Coiled spring" appearance of the proximal jejunum.

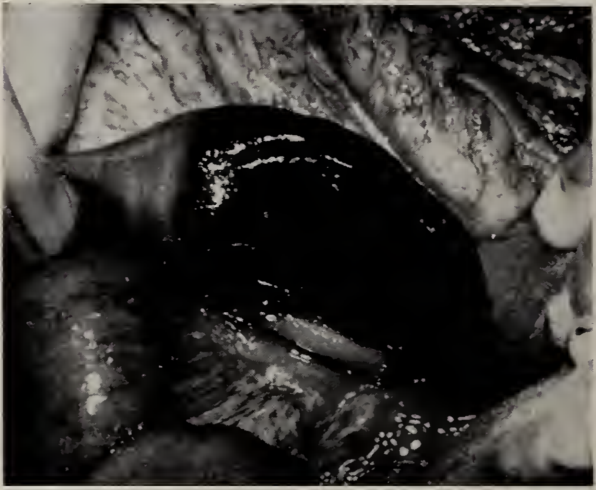

Figure 4.—Subserosal hematoma of the second portion of duodenum.

Discussion

Trauma is the major cause of intramural hematoma of the duodenum, but in 13 reported cases the lesions were attributed to pancreatitis, pancreatic tumor or hypocoagulable states, or the cause was not known.[3-8] Most of the patients are children and most are boys.[9] The higher incidence in children has been attributed to several factors—the reckless hazard of vigorous play, the greater exposure of the duodenal region owing to the wide angle of the costal arch in children, and the weaker musculature of the abdominal wall.

The relatively fixed position of the duodenum makes it susceptible to injury. In addition, physiologic areas of closure of the duodenal lumen occur at the pylorus, in the transverse portion where the duodenum crosses the spine or is crossed by the superior mesenteric vessels, and at the ligament of Treitz where the duodenum joins the jejunum. A blow to the abdomen that causes a sudden increase in intra-abdominal pressure can bring about closure of these areas and formation of a closed loop. If the force is great enough, it can cause perforation of the duodenal wall. Less forceful blows may cause disruption of the bowel wall and formation of a subserosal, intramuscular or submucosal hematoma. The tumor may remain localized or it may extend distally into the jejunum (rarely will it extend in a proximal direction). It may even dissect into the retroperitoneal area.

Two clinical syndromes have been described with this condition.[10] The majority of patients have mild symptoms of abdominal pain, often not until a few hours and sometimes days after injury. Nausea and vomiting are frequent concomitants. In a smaller group rapidly developing signs of obstruction predominate. Blood loss is usually slight. Reduction of hemoglobin or packed cell volume occurs only if the hematoma is large or there is retroperitoneal or intraperitoneal hemorrhage. Often the serum amylase is elevated, as it was in the case here reported. This is thought to be due to obstruction of the pancreatic ducts or the papilla of Vater by the hematoma, or to concurrent traumatic pancreatitis.[10-12] Jaundice due to obstruction of the common bile duct has been reported.[13]

The roentgen findings in this condition were first described by Felson and Levin.[14] On a plain film examination of the abdomen a few distended small bowel loops due to reflex ileus may be seen, or there may be evidence of a soft tissue mass within the lumen of a distended small bowel loop. Obliteration of the left psoas shadow is also frequently observed. As in the present case, evidence of extrinsic pressure on the greater curvature aspect of the stomach or on the transverse colon may be seen. A barium meal examination demonstrates the presence of an intraluminal mass within the duodenum, thickened folds of mucosa in the segment proximal to the mass, crowding of the valvulae connivents (producing the "coiled spring" appearance so frequently referred to) and obstruction to the passage of the contrast material.

There has been considerable disagreement in the literature as to the proper management of this condition.[12] There have been only four deaths reported, one of them occurring in a patient with a carcinoma of the pancreas.[6] Some investigators[2,8,15-17] advocate conservative management unless there is serious hemorrhage, complete obstruction or perforation (the latter two of which can be demonstrated by radiographic examination). Others recommend operation to evacuate the contents of the hematoma, and in some cases by-pass of the involved area.[12,18,19] Cooke and Southwood[20] mentioned exploratory laparotomy to determine whether there might be injury to other organs.

Summary

Intramural hematoma of the duodenum in a seven-year-old boy was caused by blunt abdominal trauma. In such cases the history and symptoms of a high bowel obstruction are suggestive of the diagnosis. Roentgen examination of the abdomen and of the upper gastrointestinal tract often can confirm it. Whether to treat conservatively or surgically can be determined on the basis of the clinical and radiographic findings. Signs of increasing obstruction, increasing hyperamylasemia (indicating progressive pancreatic involvement) and a decreasing hematocrit dictate surgical intervention.

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Relapsing Fever—
A Case History

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RELAPSING FEVER, a spirochetal disease transmitted by ticks, has been seen infrequently in California since the first clinical case was recorded in 1874.[1] Although the vector reservoir level remains high, the incidence of reported disease has decreased considerably, due possibly to treatment and cure of undiagnosed cases.

The present case is the only report of relapsing fever in California in 1967. Symptoms of a kind not hitherto reported occurred in both the patient and a friend of hers who had the same diagnosis.

Report of a Case

A 12-year-old girl was seen in the office on 13 August (by LS) with complaints of dizziness, headache, abdominal pain associated with generalized cramping, and fever of 39.5° C (103.2° F). On physical examination, she was thought to have an enterovirus infection and treatment was symptomatic. Clinical disease cleared after four days. Five days later it recurred with fever 40.3° C (104.4° F) abdominal and low back pain, headache, circumoral pallor and clammy skin. The patient appeared acutely ill. She was ashen, with darkly circled and sunken eyes and a distant and somewhat pained look. She appeared to have lost weight. Previously an enthusiastic, charming girl, she was now quiet, listless and without luster in appearance or speech. Where before she had been consistently inquisitive, challenging, alert and mature, she was now distant, confused and tearful without provocation. There was no significant lyphadenopathy but the abdomen was tender, especially in the left and middle regions. Neither the spleen nor liver was enlarged and there was no jaundice. There were no other significant physical findings and no tick bites were observed.

On this second visit, the patient said that she had been in the Lake Tahoe area staying in a cabin near Meeks Bay with a friend and her family. In the back of the cabin there was a high storage area which connected two rooms. The two girls had crawled through this passageway from one room to the other and had noted "rats" at the time. No one else in the family had entered this passageway. After returning home, the patient's friend was treated with tetracycline for tick bites and symptoms similar to those of our patient. Our patient had no known tick bites or evidence of ticks while at the summer cabin or at any time during her illness. Her friend's disease resolved itself without a confirmed diagnosis, although her physician had made a clinical diagnosis of relapsing fever.

Results of laboratory studies at this time included: old tuberculin negative at 1:1,000; hematocrit 37 mm; hemoglobin 12.3 gm per 100 ml; white blood cells 7,600 per cu mm with a differential of 1 percent eosinophils, 4 percent bands, 58 percent segmented cells, 34 percent lymphocytes (of which 4 percent were atypical) and 3 percent monocytes. Mean corpuscular hemoglobin concentration was 33 percent, and platelets appeared normal.

Uncorrected sedimentation rate was 46 mm in 1 hour. Results of urinalysis; of routine febrile agglutinations including Salmonella typhi O, Salmonella typhi H, paratyphi A, paratyphi B, Brucella, and tularemia; of heterophile agglutination; purified protein derivative skin test (intermediate strength); and viral studies were all negative. Viral isolation attempts were made for Q fever, typhus, Colorado tick fever, mumps, St. Louis encephalitis, western equine encephalitis, California encephalitis, and herpes simplex. All results were negative. Cerebrospinal fluid contained no cells or bacteria; glucose was 45 mg and protein 76 mg per 100 ml.

On 28 August the patient reported a new development—voices that seemed to be "screaming" in her ears, although she knew they were not really there. The voices were described as taunting, faint, and often indistinct. (Her friend had also described the same phenomenon.) She also had visual hallucinations of scenes going around in circles "like looking in a washing machine," which seemed quite real.

On 30 August she again had headache, abdom-

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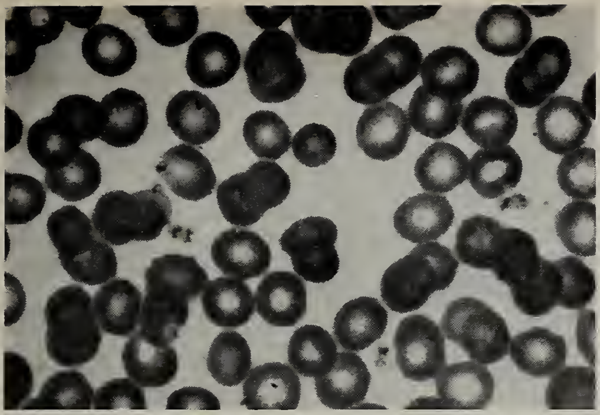

Figure 1.—Spirochete of relapsing fever (shown at center of field) on Wright stained smear of blood.

inal pain, chills and fever of 39.9° C (103.8° F). A blood smear was positive for spirochetes of relapsing fever (Figure 1). The spirochetes were observed in two separate smears (Wright stained). Penicillin was administered, 1,000,000 units intramuscularly in two doses. The patient became afebrile within eight hours after the first dose and had no further paroxysms, except that the auditory and visual hallucinations continued for six weeks with decreasing frequency.

She did poorly in school that semester, especially in reading, but when last seen had returned to her former excellent level.

Discussion

The causative agent of relapsing fever is the spirochete Borrelia duttonii, first demonstrated in 1868 by Otto Obermeier.[2] Only 50 cases have been reported in the past 15 years in California, mostly from areas above 5,000 feet. The first cases in California were at Oroville in 1874 where several hundred cases were noted among Chinese laborers.[1] The first two cases proved by laboratory procedures in California were reported in 1921 by Briggs at San Francisco County Hospital. The patients had contracted the disease in the Lake Tahoe area.[1]

The vectors are ticks of the genus ornithodoros, species hermii or parkeri.[3] Once the tick becomes infected, it remains so for years and passes the spirochete congenitally without an intermediate host. Chipmunks and tamarack squirrels are the principal reservoirs. There is usually no history of known bites. They attack humans when their usual hosts (rodents) leave the area during season changes.[4]

Diagnosis can be made at the time of an acute attack. Thick and thin smears prepared from fresh unstained defibrinated blood, mounted under a cover slip, are viewed under high-power lens. The spirochetes are about three times longer than a red cell diameter and they move vigorously. The organism may be difficult to find on a smear. (One smear in the case here reported was examined for 20 minutes before an organism was found.) Prolonged staining is helpful. Acid stains are best but Giemsa or Wright stains also work well.

The incubation period of the disease is two to 14 days (average seven) followed by onset of fever, dizziness, headache and generalized aching and chills. A macular rash which lasts two to five days may develop toward the end of the first paroxysm. Jaundice can occur and is occasionally pronounced. Attacks — as many as ten in some cases — recur at intervals of two to nine days; between attacks the patient is asymptomatic and afebrile. In untreated disease, recovery (in six to eight weeks) is related to antibody formation rather than phagocytosis; relapse is the result of ability of the organism to change antigenically.[3]

The spirochete injures all body tissue, particularly liver, spleen and kidney. During remission, spirochetes are present in splenic sinuses only, but during exacerbation they abound in peripheral blood. The disease may cause abortion in pregnant women and antibodies to it can be found in breast milk.[5] It is not communicable from one human to another.

Complications include facial paralysis, eye diseases such as iridocyclitis, vitreous opacities and optic atrophy, and possibly hypochromic anemia and leukocytosis.[6]

Prognosis is good even without treatment, although in African outbreaks fatality rates have been reported to be as high as 30 percent.[7]

Treatment with sulfonamides is ineffective; the drug of choice is probably terramycin, although penicillin may be equally effective. Antibiotic treatment should be started at the beginning of a paroxysm or after the fever has dropped, in order to avoid a "Jarisch-Herxheimer" reaction which can be dramatic and even fatal.[8] This reaction may be due to the liberation of leukocyte or endogenous pyrogen.[9] Some severely ill patients have died within hours of an intravenous dose of tetracycline or penicillin.

Two phases occur after treatment: an early pressor response (half to three hours after initial treatment) accompanied by a sharp rise in body temperature, and a late phase with a fall and then a rise in central venous and systemic arterial pressures, due most probably to myocardial damage. Gallop rhythm and electrocardiographic changes can also occur.[7]

The disease must be differentiated from other febrile illness, particularly Weil's disease, typhus fever and atypical pneumonia. At the onset it can mimic a common viral infection, as it did in the present case.

Summary

A case of relapsing fever in a 12-year-old girl who acquired it in the Lake Tahoe area of California is reported. Hallucinatory symptoms, not a frequent concomitant, were noted in addition to the usual symptoms. Diagnosis was made by examination of blood smears after three recurrences of symptoms in a two-week period. After treatment with penicillin, symptoms abated and did not recur.

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COUNSELING TEEN-AGERS ABOUT DRUG USE

How do you counsel the teen-ager about drug abuse?

"I don't believe there is much difference between counseling a patient who is using drugs as a way of trying to solve an emotional problem, and counseling anyone else. I think, though, that the thing to do is to avoid focusing on the drug problem per se.

"It's unusual for a patient to come in complaining of having a "drug problem." Most patients come because they're having problems with depression, or poor concentration, or some kind of anxiety; and they don't mention the use of drugs, except in passing. I think it's important for the pediatrician to be as objective as possible about the drug situation when it comes up in the course of a counseling interview and not to become alarmed and begin moralizing on the subject or making threats about reporting the patient to his parents, or the police, or the school. Nor should he try to bludgeon the patient into promising to give up using drugs. I think that the pediatrician is better off if he presents the facts as he knows them, outlines the risks involved in using drugs, and then leaves it up to the patient to make the decision as to whether or not he stops using them. After that he should go quickly into a discussion of the psychological problems the patient has in the area of his school work, his relationship with his parents, his relationship with girl friends, and his difficulties in athletics. This is where the basic problem lies; and if the patient can resolve these problems, he is going to give up drugs spontaneously."

—GRAHAM B. BLAINE, JR., M.D., Boston

Extracted from *Audio-Digest Pediatrics,* Vol. 14, No. 21, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

Clinical Aspects of Temporal Lobe Epilepsy—A Review

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■ *Temporal lobe epilepsy appears to be of increasing concern to psychiatrists, pediatricians and lawyers as an explanation for some aspects of behavior. There is a high incidence of structural abnormality associated with temporal lobe epilepsy, the most common being mesial temporal sclerosis. Depth electrode studies have shown that the most common focus for the clinical seizure is in the hippocampus or hippocampal gyrus. The first line of treatment continues to be attempt at control with anticonvulsant agents. Surgical treatment can be offered, in many instances, when drug therapy has failed.*

THOUGH ONE OF the oldest diseases known to man, epilepsy entails diagnostic problems that become more complicated with the growing recognition of its many clinical aspects and diverse presentations. One particular kind of convulsive disorder, temporal lobe epilepsy, may be particularly difficult to identify because of its complexity and the bizarre behavior exhibited during an attack. This review of psychomotor or temporal lobe epilepsy is designed to emphasize common clinical features that assist in its recognition, for the disorder is prevalent enough to be encountered occasionally by all physicians.

There are several reasons why such a review might be considered appropriate at this time. Temporal lobe epilepsy received considerable notoriety in a famous murder trial in Texas, and continues to be proposed as a medical-legal defense in criminal actions involving aggressive acts. Psychiatrists are becoming increasingly aware of the disorder and many now include the convulsive phenomenon of this type in the differential diagnosis of transient, usually irrational and aggressive behavior. Pediatricians, who are confronted with the variety of behavior disorders that occur in children, also consider temporal lobe epilepsy as an occasional diagnostic possibility if we may judge by the requests received in most electrocardiographic laboratories.

In the past decade, a greater precision has been developed in identifying the dimensions and subtleties of this disorder. This has taken place largely through the process of greater clinical experience of a number of neurologists, with the result that there now appears to be a nearly complete catalogue of all the signs and symptoms occurring in temporal lobe epilepsy. Contributions to the better understanding have also been made by a more sophisticated use of electroenceophalography both as a clinical tool and as a research technique. It has been possible, for example, to implant depth electrodes into the temporal lobe areas of some patients who are being considered for surgical treatment and thus directly correlate their ictal behavior with the electrical changes in the brain. Telemetering of the EEG signals from the depth of

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the brain also permits a further opportunity to verify unusual behavior associated with seizures, which in the past was assumed only by inference to be related to seizure.

Clinical Features

The majority of temporal lobe seizures can be categorized and described by the most common sequence of the attack. Beginning with the aura, the spell progresses to a phase demonstrating autonomic phenomenon, then the automatism, finally terminating in a limited number of ways. Most patients have fairly stereotyped attacks, although in general there are much greater differences between patients than in generalized tonic-clonic seizure.

The Aura. This warning in temporal lobe epilepsy is the most elaborate and complex of all seizure types. It may range from a relatively non-specific feeling, such as the rising of the epigastric sensation, to the familiar déjà vu experience, to a detailed dream-like sequence. The aura, if present, is remarkably stable from seizure to seizure. Some examples of the variety of experiences reported by patients during this phase are as follows:

> *"It's the most intense feeling of fear and dread you could possibly imagine—not fear of anything—just fear."*
>
> *"Don't laugh at this, and you will think I'm crazy when I tell you, but I see a sort of Mickey Mouse—a figure with large round ears, black with a white nose—just like on my watch when I was a kid."*
>
> *"It's like watching TV, I can see myself, in color, going to a window and looking out at a scene of green grass, a brook, an oak tree—always the same thing over and over again."*

In general, the aura of memory type appears trivial to the patients in that they cannot relate the scene or sequence to any significant life experience. It is also possible that the patient has an aura, but is amnestic for the details as he is for the subsequent automatism. An example of this may be expressed in the following comment by a patient:

> *"I can never remember just what it is. It think that there are voices that I can hear, like from another room, but I can't make out just what they are saying."*

Understandably, patients are often reluctant to discuss their aura for fear that it will have the same connotation to physicians as hallucinatory experiences of other types.

Autonomic Phenomenon. At nearly the same time as the aura, or shortly afterward, the patient may exhibit pallor, flushing, or pilo-erection or have an urgent desire to void or defecate. Though not strictly an autonomic function, respiratory arrest may occur and it has been observed for as long as 40 seconds. Salivation has also been witnessed in this early stage of the attack. Other patients have reported that their heart rate accelerates, and they become aware of a pulsatile throbbing in the ears.

Automatic Behavior. A brief period, generally seconds, elapses between the aura and the loss of awareness. The automatism is less stereotyped than the aura and is in part dependent upon the environmental setting. Automatic behavior appears as inappropriate to the situation, is often bizarre, and is recognized as abnormal by most lay observers. Lip smacking is extremely common during or at the onset of this stage and witnesses often say of the patient that he appeared "as though he were chewing his tongue." This description may be misleading, for it has implications of a generalized seizure. However, a simple demonstration by the examiner of the typical lip smacking and mouthing movements frequently evokes the comment: "Yes, that's it—that's just what he does."

The automatism may be associated with mumbled, incoherent speech with speech arrest, or stereotyped or repetitive phrases. A 45-year-old man was heard to say "Mother, Mother, Mother" and an admitted agnostic repeatedly uttered "God, God—oh, my God." Some multilingual persons have been known to verbalize only in their first learned language.

Some examples of the behavior observed during an automatism are provided by the following:

A modest matron suddenly had a dazed expression, began smacking her lips and pulled up her skirts to conspicuously adjust her girdle. This was quickly followed by a fumbling with the buttons on her blouse, the total episode lasting about 30 seconds. Although this occurred in mixed company, she appear to have no recollection of the event immediately afterward.

While being interviewed, another patient suddenly became silent, looked about the room in a perplexed way, then climbed upon his chair. From this position he stepped over to a desk, walked along its top but avoided objects on the desk. He appeared oblivious to the observer's entreaties to come down. Afterward, he was amnestic for the event and incredulous when it was described to him.

Obviously such behavior may evoke a wide variety of differential considerations in diagnosis.

However, a practical point to be stressed in distinguishing an ictal automatism from a fugue or dissociative state is the duration of the episode. In all the spontaneous attacks that I have personally witnessed and also in those that have been induced by the electrical stimulation of sites within the temporal lobe, the duration has been from about 15 seconds to 2 minutes. Episodes of longer duration have been described but they are distinctly uncommon. In contrast, a dissociative reaction may have a duration of many minutes, or hours or even days.

I have never witnessed aggressive behavior in the form of a specifically directed attack during automatism. Attempts to restrain the patient during the course of automatism, however, may give rise to a sort of poorly organized, poorly directed resistance. This generalization would appear to be the commonly accepted position of most neurologists.[1]

Termination of the Seizure. The temporal lobe seizure usually abruptly stops during the phase of automatism. The patient "comes to," looks about in a puzzled fashion, may express surprise at any new relation with his surroundings, and is only momentarily confused. This is in contrast to the more prolonged post-ictal confusion and the period of sleep that so often follow generalized tonic-clonic seizures.

In some instances, the temporal lobe attack continues into a generalized, major motor seizure with the classical features of tonic-clonic activity, including sometimes incontinence and self-injury. It is possible, then, to have two periods of confused, bizarre behavior — the first at the onset of the attack, as represented by the automatism, and the second at the end of the tonic-clonic seizure. Status temporal lobe epilepticus is quite rare.

Age of Onset. Seizures that can be identified as psychomotor in type on the basis of the above description rarely occur in anyone less than five years old. They may appear between the ages of five and ten years, but most often after age ten.

Association with Seizure of Other Types. Not often does one see a patient who has only "pure" temporal lobe seizures and has never had any other kind of convulsion. Most patients have a mixed seizure history, though the temporal lobe seizure may be the dominant or most frequent one. About one-fourth of the adult patients have a childhood history of petit mal seizures that stopped in the mid-teens, with both generalized tonic-clonic seizures as well as temporal lobe attacks developing later. Nearly a fourth of the adult patients also have a history of febrile seizures.

Pathophysiologic Basis for Seizures

Temporal lobe convulsive disorder is associated with a high incidence of neuropathological findings. On examination of surgically resected temporal lobes, Falconer and Taylor[2] noted such changes in 75 percent of specimens, and Green[3] in 84 percent. The incidence of pathological changes in an autopsy series was about 50 percent.[4,5]

"Incisural" or "uncal" or "mesial" temporal sclerosis is the most common neuropathological finding, as has been noted since Sommer's[6] description in 1880. However, the mechanism for this dropping out of neurons and replacement by glial tissue is not clear and a variety of theories have been proposed, ranging from herniation of the uncus during the molding of the head at birth,[7] to hypoxia secondary to other types of seizures,[5] to sub-clinical viral encephalitis during childhood and to developmental anomalies of the temporal lobe.

Other, but less commonly encountered, pathological findings are small, slow-growing neoplasms such as hamartomas or astrocytomas, small arterial-venous malformations, temporal lobe convexity scars, or gross structural anomalies of the temporal lobe. At least commonly enough to shake the neurologist's complacency, a large infiltrative primary brain tumor is encountered even in cases in which the history of seizures extends over many years.

The focal origin of the electrical seizure in this disorder has been clearly demonstrated by the use of chronically implanted depth electrodes.[8,9] A clinical temporal lobe seizure can almost always be seen to originate electrically in the hippocampus or the hippocampal gyrus, rarely in the amygdala, and not, in our experience, from temporal lobe convexity cortex. Figure 1 illustrates the focal origin of a clinical seizure by means of chronically implanted electrodes. The results of these studies would also indicate that although the seizure begins in these deep structures, the electrical event must propagate to other structures before a clinical seizure develops.

Diagnostic Considerations

As in most neurological disorders, the history supplies the major evidence for establishing a diag-

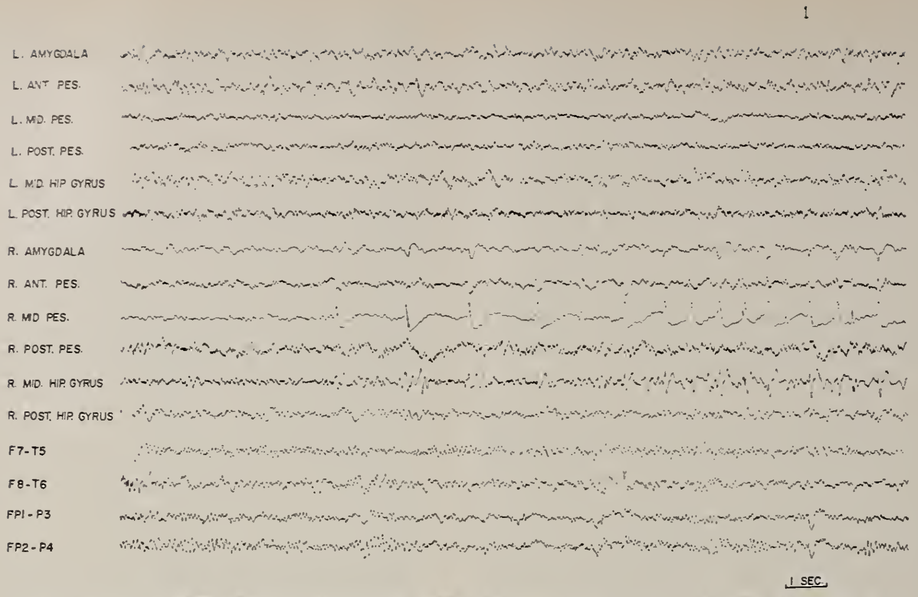

Figure 1.—This 20 second recording was obtained from both the deep structures in the left and right temporal lobe and from the scalp. The first six channels are from the left depth, the next six channels from the right, and the last four are from the scalp. Channel 9, from the right mid pes hippocampi, records a series of focal spikes that increase in their frequency of appearance that precedes a clinical temporal lobe seizure by some 20 seconds. It might be noted that there is no reflection of this spiking activity in the scalp recordings.

nosis. However, the patient with seizures is a poor witness because of the lack of awareness during phases of the attack. The only source of information about the aura is the patient, but he cannot be expected to supply primary information about his automatism. Most patients offer a second-hand report based on the descriptions of others, but it is always a good practical rule to interview an observer who has witnessed a seizure.

Additional diagnostic support may be provided through the EEG. Eighty-five percent of our patients have had a focal electrical abnormality, usually a spike discharge, appearing over one or both temporal lobes. The detection of this electrical sign is greatly facilitated by recording from the patient both during the waking state and during sleep.

In view of the now recognized high incidence of structural changes associated with this disorder, the neurological strategy is changing in the direction of a more complete evaluation of these patients. While it is true that the most common lesion—mesial temporal sclerosis—cannot be detected by conventional techniques, the possibility of a larger lesion must be kept in mind, particularly with the history of seizures appearing in adult life. This evaluation includes a careful neurological examination, x-ray studies of the skull, brain scan, and spinal fluid examination. Contrast procedures may be indicated, depending on the particular clinical problem.

There are a large number of both common and esoteric neuropsychiatric disorders that are frequently involved in the differential diagnosis of temporal lobe epilepsy. The hallucinatory quality of the aura may suggest a psychotic process, the automatism may resemble a fugue or dissociative state, and the halo of bizarre conduct suggests hysteria. Even the night terrors of children, observed by sophisticated parents, have been thought to represent temporal lobe epilepsy.

Treatment

Anticonvulsant drug therapy continues to be the major resort in the treatment of this disorder. As in the treatment of convulsive disorders of other types, the selection of the appropriate drug can only be broadly prescribed and the specifics depend largely on trial and error. The major anticonvulsants for this kind of seizure continue to be diphenylhydantoin, phenobarbital and primidone, although control can be achieved by the addition of many other anticonvulsants. As a practical point, it is advisable to indicate to the patient that this quest for the appropriate agent or agents in the right amount may take a considerable period. Failure to control the attacks in spite of an extensive trial of anticonvulsants can be expected in an estimated 30 to 40 percent of the patients.

When confronted with failure of drug therapy, consideration should be given to the possibilities of surgical treatment. It should again be pointed out that temporal lobe epilepsy is associated with a high incidence of structural alterations. The problem, however, from a surgical point of view, is the selection of the appropriate side for resection. This decision can at times be facilitated by the results of contrast procedures, but more commonly depends upon the results of special electroencephalographic studies that are becoming increasingly available in medical centers across the country.

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WHAT SHOULD THE PARENTS DO ABOUT DRUG USERS

"One of the stickiest problems related to drug usage in children is the parent who calls you and says that he knows his boy is taking drugs and he can't get the boy to come and see you. He wants to know how he should handle the situation. Should he call in the police, should he call up the school, or what should he do?

"Parents in situations like this should not call in the police. I think they should warn their child—if they can collar him long enough for a conversation—that this may happen through other channels, but they should not take the initiative in doing this. I don't think they should report him to the school either. What they should try to do first is persuade him to go and see a doctor or, failing that, some person outside the family—because clearly if he doesn't go to a doctor right away there is not good communication within the family. If the parents absolutely can't persuade him, then I think they should avail themselves of every opportunity to talk with him. They should continue to try to get in communication with the child—if not on this particular issue, then on some other issue."

—Graham B. Blaine, Jr., M.D., Boston
Extracted from *Audio-Digest Pediatrics,* Vol. 14, No. 21, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

MEDICAL STAFF CONFERENCE

Lactic Acidosis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Associate Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. BOUSHEY:* A 31-year-old Caucasian male was admitted to the Neurology Service because of weakness. Following trauma to the left ear at age 9, he noticed progressive deafness. At age 11 he was said to have an abnormal gait. At age 24 he first began wearing a hearing aid.

Since age 17 he has noted "dizzy spells" characterized by twitching of the left forearm but not associated with loss of consciousness. One year before admission to this hospital he had two fainting spells which could not be characterized further. In the past three years his weight had decreased 30 pounds and he had noticed progressive wasting and weakness in both the upper and the lower extremities. Also he reported having five soft bowel movements a day since visiting British Honduras 18 months before hospital admission.

At age 22 the patient began to have polydipsia and polyuria and was found to have diabetes mellitus. He was treated initially with regular insulin, but soon thereafter treatment was changed to phenformin, 50 mg three times a day, a treatment that was still being followed at the time of admission to hospital. His family history is strongly positive for diabetes: His father, maternal grandfather and two maternal aunts had maturity-onset diabetes.

Physical examination: Funduscopic examination revealed retinitis pigmentosa, arteriolar narrowing, waxy exudates, and numerous microaneurysms. Results of examination of the heart, chest, and abdomen were within normal limits. The testes were soft and small. Both plantar arches were noted to be high. Other abnormalities, confined to the neurologic system, included bilateral neurogenic hearing loss, weakness of both shoulder and hip girdle muscles, cerebellar signs with ataxia, and bilaterally hyperactive knee jerks with positive Babinski responses bilaterally.

Laboratory studies: Packed cell volume 35 percent, leukocytes 6,700 cells per cu mm, urine pH 6.0, 24-hour urine protein 2.6 grams. The urine was negative for ketone bodies. Serum sodium was 135, chloride 102, carbon dioxide 23, and potassium 5.4 mEq per liter. Serum creatinine was 1.6 mg per 100 ml, and creatinine clearance was calculated at 25 ml per minute. Total serum protein was 6.3 grams per 100 ml, cholesterol 326 mg per 100 ml, and uric acid 7.8 mg per 100 ml. Serum protein electrophoresis was within normal limits. A chest radiograph and an electrocardiogram were within normal limits.

Five days after admission the patient vomited three times and passed three soft-formed stools. He remained afebrile but became tachypneic and appeared dehydrated. At this time serum sodium was 140, chloride 100, potassium 6.7, and carbon dioxide 7.0 mEq per liter, yielding an anion gap of 33 mEq per liter. Blood glucose was 127 mg per 100 ml and serum acetone was negative. The packed cell volume had risen to 45 percent, and the leukocyte count was 13,200 with 80 percent

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*Homer A. Boushey, Jr., M.D., Intern in Medicine.

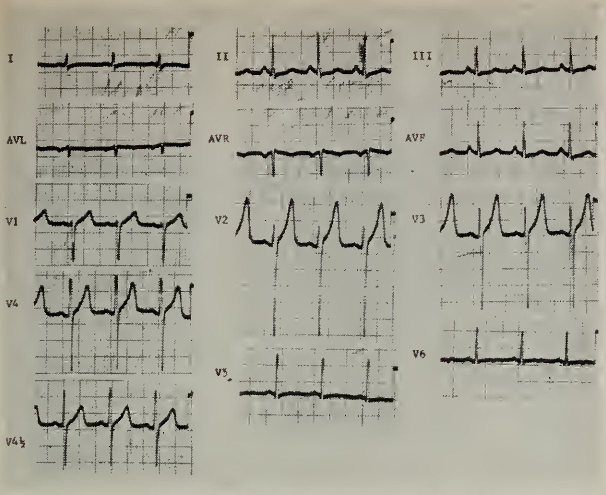

Figure 1.—Electrocardiogram showing peaking of T-waves in leads V_2-V_4.

polymorphonuclear forms. Six hours later the serum sodium was 140, chloride 98, potassium 7.8, and carbon dioxide 5.0 mEq per liter, yielding an anion gap of 37 mEq per liter. Arterial pH was 7.17. Blood glucose was 122 mg per 100 ml, and acetone was not present in the serum.

A repeat chest radiograph was within normal limits, but a repeat electrocardiogram (Figure 1) showed peaking of the T-waves in leads V_2 through V_4.

The total bicarbonate deficit was calculated at approximately 370 mEq, and treatment was initiated with intravenous dextrose and 0.5 normal saline solution with 90 mEq of sodium bicarbonate. After a total of 100 mEq of sodium bicarbonate was administered, serum sodium was 133, chloride 95, potassium 5.7, and carbon dioxide 5.0 mEq per liter. Serum acetone was still absent. After a total of 180 mEq of sodium bicarbonate, the serum potassium had fallen from 5.7 to 4.0 mEq per liter, and the carbon dioxide had risen from 5.0 to 10 mEq per liter. After 225 mEq of sodium bicarbonate, serum sodium was 133, chloride 100, potassium 4.0, and carbon dioxide 28 mEq per liter. Serum creatinine had risen to 1.9 mg per 100 ml, the blood urea nitrogen to 153 mg per 100 ml. The intravenous fluids were discontinued on the following morning and the patient felt well. Phenformin therapy was discontinued and insulin therapy begun. The serum lactic acid level during the acute episode was increased, confirming a diagnosis of lactic acidosis.

DR. SMITH:* Thank you very much, Dr. Boushey. The patient is here for presentation. I am afraid the factors of greatest interest to us today will not be revealed by physical examination. (Patient enters.) How are you feeling today?

PATIENT: I am feeling better, much better.

DR. SMITH: What was the main problem that was bothering you when you came to the hospital?

PATIENT: When I entered the hospital I had diarrhea. It started about a year ago.

DR. SMITH: Dr. Williams, do you have any points you would like to bring out on history?

DR. WILLIAMS:† I wanted you to tell us when the diarrhea improved.

PATIENT: A week ago.

DR. WILLIAMS: What happened at that time?

PATIENT: My medications were changed.

DR. WILLIAMS: Phenformin was stopped and insulin therapy begun at that time. His physical findings are not apparent at present. They are confined to the neurological examination and to the examination of the eye.

DR. WILLIAMS: Thank you for coming in. (Patient leaves.)

DR. SMITH: The discussion this morning will not be related to the patient's neurological deficit nor to his diabetes *per se,* but to the peculiar form of acidosis which was the most striking feature of his clinical course in the hospital. Dr. Williams has been particularly interested in this form of acidosis and has measured the levels of lactic acid in this patient. I would like to ask him to open the discussion.

DR. WILLIAMS: In summary, this patient is a 31-year-old male with a congenital neurologic disorder characterized by mental retardation, retinitis pigmentosa, deafness, cerebellar ataxia, and myopathy. He also has juvenile diabetes mellitus with onset at age 22 and has been treated for the last nine years with phenformin, 150 mg per day. After admission to the hospital and while apparently feeling quite well, he had sudden onset of severe acidosis with a significant anion gap. I would like to discuss two aspects of this patient's clinical problem: (1) the cause of the acidosis and (2) the relationship of this acidosis to the phenformin therapy.

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*Lloyd H. Smith, Jr., M.D., Professor and Chairman, Department of Medicine.

†Hibbard E. Williams, M.D., Associate Professor of Medicine.

TABLE 1.—*Acidosis with Anion Gap—Causes.*

Diabetic ketoacidosis
Uremic acidosis
Drug ingestions
Lactic acidosis

Acidosis with an Anion Gap

The causes of acidosis associated with an anion gap are shown in Table 1. The most important form of acidosis of this type is diabetic ketoacidosis. In this clinical situation the anion gap is related to the presence in the serum of increased amounts of ketone bodies, particularly β-hydroxybutyrate and acetoacetate. Although this patient did have diabetes mellitus, it is clear he did not have ketoacidosis. He did not have serum acetone measurable at any time during the episode of acidosis.

The second cause of this syndrome is uremic acidosis. This is another very common cause of acidosis associated with an anion gap. Patients with uremic acidosis have accumulation of sulfate and phosphate as well as certain organic acids in the serum, some known but some as yet unidentified. Lactic acid may be elevated in the serum of patients with uremic acidosis.

The third consideration is drug ingestion. Here I refer specifically to salicylate poisoning, where acidosis is seen commonly. The anion in this situation is lactate. Paraldehyde ingestion has been associated with acidosis, but the mechanism for the acidosis is not well understood. Methanol and ethanol in excessive amounts produce severe acidosis with accumulation of other anions. With ethanol ingestion this probably represents lactate as well as acetate. In methanol ingestion, formate is probably the more important anion. Finally, ethylene glycol ingestion has been associated with acidosis and an anion gap.

The fourth category, lactic acidosis, is exemplified by the problem seen in the patient presented today. This patient had abrupt onset of acidosis. At that time the serum level of lactate was measured at 17 micromoles per ml, which is approximately ten to fifteen times the normal level of 1 micromole per ml. (A pyruvate level was not estimated.) At the time this lactic acid level was drawn, the anion gap was estimated at approximately 35 mEq. With the addition of this lactate concentration to the sum of the chloride and the carbon dioxide concentrations, the anion gap returns to the normal range. Hence, that lactate recovered in the serum of this patient accounted totally for the anion gap.

Lactic Acid Metabolism

Before commenting on the clinical syndrome of lactic acidosis, I would like to discuss a few features of lactate metabolism. Lactate is produced as an end-product of anerobic glycolysis. It is produced by nearly all tissues in the body but particularly by skeletal muscle and erythrocytes. Metabolism of lactate occurs primarily in the liver by oxidation to pyruvate in the presence of lactic dehydrogenase. The hydrogen receptor for this reaction is NAD (nicotinamide adenine dinucleotide) which is reduced to NADH as oxidation of lactate occurs. Although this reaction is reversible, the equilibrium of the reaction strongly favors the reduced product lactate so that the normal lactate-pyruvate ratio is approximately 10:1 (that is, for one mole of pyruvate there are approximately ten moles of lactic acid). The subsequent metabolism of lactate is dependent upon the metabolism of pyruvate. There are two major pathways for pyruvate metabolism: (1) oxidative decarboxylation to acetyl coenzyme A in the Krebs cycle and (2) conversion to phosphoenolpyruvate on the gluconeogenic pathway to glucose. Regardless of the underlying defect, the accumulation of lactic acid in blood must result from one of two mechanisms: (1) increased production of lactate or (2) decreased utilization of lactate. Increased production is observed in situations associated with increased glycogenolysis, particularly muscular exercise, hyperventilation, and administration of glucagon, epinephrine, or fructose. Much less is known about the utilization of lactate. Decreased lactate utilization probably occurs whenever tissues are unable to oxidize lactate to pyruvate, to oxidize pyruvate sufficiently rapidly in the Krebs cycle, or to convert pyruvate to glucose by the gluconeogenic pathway.

The accumulation of lactate is always associated with the appearance of an equivalent number of hydrogen ions. Regardless of the arterial pH, in the subsequent discussion when I refer to lactic acidosis I imply lactate accumulation with or with-

TABLE 2.—*Lactic Acidosis—Classification.*

- I. Primary
- II. Secondary
  - A. To diseases associated with hypoxemia
  - B. Idiopathic

out acidosis, since the buffering ability of the blood may maintain arterial pH within the normal range despite the presence of increased amounts of lactate.

The Clinical Syndromes Associated With Lactic Acidosis

Table 2 outlines the classification of the lactic acidosis syndromes in man, based on Huckabee's classification.[1,2] Group I, the so-called primary type, refers to those situations in which the accumulation of lactate is in response to an overproduction of pyruvate with an appropriate amount of lactate being formed. Such situations include muscular exercise, hyperventilation, and administration of glucagon or epinephrine. In this group acidosis is usually not present and the lactate-pyruvate ratio is normal, 10:1.

Patients included in the category of Group II have lactic acidosis secondary to some underlying disease process. In Group IIA lactic acidosis is associated with those diseases in which hypoxemia plays a major role (acute hemorrhage, severe circulatory collapse, cyanotic congenital heart disease, and severe congestive heart failure). In these patients the serum lactic acid level is quite high, the lactate-pyruvate ratio is increased (implying accumulation of lactate in excess of that expected from the amount of pyruvate present), and acidosis may be quite severe.

Group IIB, referred to as idiopathic lactic acidosis, includes those patients who have sudden onset of lactic acidosis in the absence of an underlying disease process or precipitating event. The acidosis seen in the patient presented this morning is probably best classified as idiopathic lactic acidosis. He was feeling well in the hospital, he had no hypotension or hypoxemia, his appetite was good, and except for mild diarrhea he had no complaints. Suddenly one evening severe vomiting developed and the complete picture of lactic acidosis was documented. The onset of this syndrome was sudden without an obvious precipitating event.

Table 3 outlines some of the clinical characteristics and laboratory findings of spontaneous idiopathic lactic acidosis. Onset is rapid, often in a matter of hours as was the case with this patient. The specific clinical features include (1) changes in the state of consciousness and (2) signs of hyperventilation. Changes in the state of consciousness may vary from mild lethargy to stupor and eventually to coma. The mortality of the syndrome has been directly related to the degree of impairment in the state of consciousness. Hyperventilation, representing respiratory compensation for the severe metabolic acidosis, is identified by the presence of Kussmaul breathing. As has been pointed out by others,[3] hyperventilation *per se* may lead to lactate accumulation. The question of whether hyperventilation is secondary or primary has not been resolved in all patients. There is a very high mortality associated with this syndrome; in approximately 75 percent of the recorded cases the patients died. Death usually occurs rather soon after onset of the syndrome, usually in a matter of hours or days.

TABLE 3.—*Lactic Acidosis—Clinical Characteristics.*

Acute onset
Changes in state of consciousness
Hyperventilation
High mortality
Low serum bicarbonate and pH
Elevated serum potassium
Normal or low serum chloride
Anion gap
Elevated blood lactate and increased L/P ratio
Other abnormal findings

The laboratory features of the disease are characteristic. As one would expect, the serum bicarbonate level is low. In the recorded cases this has varied from 5 to 15 mEq per liter, usually closer to 5 than to 15. The serum pH is appropriately reduced and has varied from 6.98 to 7.25. The serum potassium is usually elevated in the range of 6 to 7 mEq per liter, representing a secondary response to the extracellular acidosis. The serum chloride is usually normal, although it may be somewhat depressed. The serum sodium is likewise usually normal. When the sum of the sodium and potassium cations exceeds the sum of the chloride and bicarbonate anions by greater than 15 mEq, an anion gap is said to exist. As the name of the syndrome implies, the blood lactate levels are elevated above the normal level of 1 micromole per ml. After muscular exercise one may see an increase in blood lactate levels to 4 or 5 micromoles per ml. In patients with spontaneous idiopathic lactic acidosis, however, the serum lactate level usually exceeds 7 micromoles per ml and may rise as high as 30 micromoles per ml (approximately 270 mg of lactate per 100 ml of blood). Coincidental with this increase in blood lactate is an increase in the lactate-pyruvate ratio, sometimes to as high as 60:1. Other abnormal findings include marked leucocytosis, an increase in the serum glutamic-oxaloacetic transaminase level perhaps related to changes in the liver blood flow, and an

TABLE 4.—*Lactic Acidosis—Associated Conditions.*

Chronic renal disease with uremia
Infection—septicemia
Diabetes mellitus
Pancreatitis
Cirrhosis
Pregnancy
Cardiovascular disease

increase in the level of serum phosphate as noted by Tranquada.[4,5]

Table 4 outlines the underlying diseases or associated pathological conditions which have been noted in patients with idiopathic lactic acidosis. These disorders are not thought to be a primary cause of lactic acidosis in patients in whom this syndrome has been reported. It is quite possible, however, that in the proper circumstances any one of these conditions could lead to lactic acidosis. The most common association is chronic renal disease with uremia. Actually in most patients the renal failure is fairly mild; most of the patients have only modestly lowered creatinine clearances. There have been only a few patients with severe uremia and associated uremic acidosis in addition to lactic acidosis. Infection has been a very common feature. This includes infection in the skin, in the lung, and particularly in the urinary tract. Acute pyelonephritis represents one of the more commonly associated conditions. Septicemia with Gram-negative organisms has been a problem in some of these patients.

Diabetes mellitus is also a frequent complication in patients with lactic acidosis. Both growth-onset and maturity-onset forms of diabetes have been described with lactic acidosis. The association of lactic acidosis with phenformin therapy is discussed below. Cirrhosis has been found in a small number of patients, and acute pancreatitis has been a problem in some. There appears to be an increased incidence of this syndrome in pregnancy, particularly in the third trimester and at the time of delivery. Finally, some patients have had severe cardiovascular disease, especially coronary artery disease and peripheral ischemic vascular disease. Although these are thought to be associated conditions, their role in the primary precipitation of lactic acidosis is not really defined.

TABLE 5.—*Lactic Acidosis—Treatment.*

Decrease hypoxia
Correct dehydration and hypovolemia
Maintain blood pressure
Correct acidosis
Dialysis

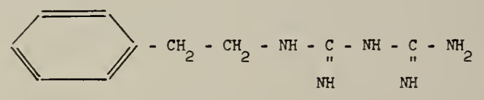
Table 5 outlines in rather naive form the treatment of lactic acidosis. Obviously any hypoxia should be decreased, with use of oxygen and intermittent positive pressure breathing if necessary. It is important to maintain an adequate circulating blood volume, and hypovolemia must be treated actively. A central venous pressure catheter is particularly useful in evaluating adequacy of volume replacement. Although the maintenance of blood pressure is important, vasoconstrictive agents should be avoided since the effect of some of these agents on muscle blood flow may lead to a worsening of lactic acidosis due to relative hypoxemia of the skeletal muscles.

The fourth point is obvious and important—namely, correction of the acidosis. It should be done quickly with large amounts of bicarbonate given intravenously. Often doses of bicarbonate greater than 200 to 400 mEq are necessary for complete correction of the acidosis.[6] The use of intravenous fluids containing lactate should be avoided in the treatment of this type of acidosis. It is important to monitor the serum potassium level during the treatment of the acidosis, as the serum potassium level tends to fall with abrupt alkalinization. Tranquada[7] suggested the use of methylene blue in these patients. Methylene blue is capable of oxidizing reduced NADH to NAD, thereby shifting the equilibrium of lactate toward pyruvate. Tranquada used this in a few patients with some apparent success, but it has not been evaluated on a large scale. Dialysis has been suggested and has been used in some patients, but it is difficult to explain its effectiveness, particularly since many dialysis fluids contain lactate. As noted, the prognosis for patients with this syndrome is poor; despite therapy, 75 percent of the patients reported in the literature have died.

Lactic Acidosis and Phenformin Therapy

What is the relationship of the lactic acidosis in this patient to the phenformin therapy? Figure 2

Phenformin



Metabolism - none

Excretion - kidney

Mechanism of action - inhibition of oxidative phosphorylation
inhibition of gluconeogenesis

Figure 2.—Pharmacologic features of phenformin.

outlines some important pharmacologic features of phenformin. This oral hypoglycemic agent is one of the class of biguanide compounds known for some time to produce hypoglycemia. Note that it is not a sulfonylurea drug. It is absorbed well from the gastrointestinal tract. It is probably not metabolized in man; a single dose of phenformin will be excreted unchanged in the urine and feces in 24-48 hours. Excretion by the kidney is a very important feature which should be emphasized. The blood level of phenformin is very dependent upon the glomerular filtration rate and will increase remarkably in the presence of renal insufficiency. Speculations as to the mechanism of action of phenformin have been discussed for a number of years. Phenformin produces hypoglycemia only in diabetic patients; it is not effective in producing hypoglycemia in normal subjects.

Two major mechanisms of action have been proposed. Historically, inhibition of oxidative phosphorylation has been considered the major site of action. This has been demonstrated by *in vivo* and *in vitro* studies in experimental animals.[8] Presumably phenformin inhibition of NAD-dependent pyruvate oxidation, or the cytochrome oxidase system, leads to an increase in anerobic glycolysis and thereby to a secondary increase in glucose uptake in peripheral tissues such as muscle. Because rather large amounts of drug are necessary to inhibit oxidative phosphorylation in experimental studies, it has been questioned whether this mechanism is important in diabetic subjects receiving relatively modest doses of the drug. More recently a second mechanism of action has been emphasized —that of inhibition of gluconeogenesis.[9] *In vivo* and *in vitro* evidence of phenformin inhibition of gluconeogenesis from such substrates as lactate, pyruvate, alanine, and serine has been demonstrated. The exact site of inhibition of gluconeogenesis is unknown. An important feature of this mechanism is its demonstration at relatively low concentrations of drug—those obtainable in diabetic subjects receiving the usual recommended doses of phenformin. It seems likely that this is the more important mechanism of action of this drug in man.

The relationship of phenformin to lactic acidosis in diabetic subjects is not clear. Most of the diabetic patients in whom lactic acidosis has developed while they were taking phenformin had growth-onset diabetes. All of those reported have had some renal insufficiency, and in many it was quite severe. The onset of the lactic acidosis was sudden as it was in the patient presented today. It has been suspected for a number of years that phenformin was the precipitating agent in the acidosis. A problem exists in this explanation. As many physicians have pointed out, most diabetic patients treated with phenformin do not accumulate lactate, and secondly, spontaneous lactic acidosis occurs in diabetes mellitus without the use of phenformin. However, it is possible to speculate on the association of this syndrome with phenformin therapy in certain diabetic subjects. Since all diabetic patients reported with this syndrome have had renal insufficiency and since the excretion of phenformin is dependent on a normal glomerular filtration rate, it is likely that phenformin gradually accumulates in the blood of these patients until it reaches a level capable of inhibiting oxidative phosphorylation. Under these conditions lactate would accumulate, eventually resulting in the clinical picture of lactic acidosis.

I think this situation may have occurred in the patient presented today. He has some renal insufficiency as evidenced by a creatinine clearance of 25 ml per minute. Although he was treated with phenformin for a very long period, it is conceivable that the development of renal insufficiency, perhaps as a result of Kimmelstiel-Wilson disease, led to the gradual accumulation of phenformin in the blood and the precipitation of an episode of lactic acidosis.

In summary, I believe this patient represents an instance of spontaneous lactic acidosis in man—probably secondary to phenformin therapy. He responded well to bicarbonate therapy and removal of phenformin. Unfortunately, I am unable to speculate on the relationship of this metabolic disturbance to the underlying neurological disorder in this patient. Perhaps this latter problem will form the basis of another Grand Rounds exercise in the future.

DR. SMITH: Thank you very much, Dr. Williams. We have time for questions or comments. Dr. Michael Berry is an expert in this area and has had long interest in it.

DR. BERRY:* Perhaps I should congratulate the patient on his recovery rather than the physicians, because I really think the patient deserves most of the credit. You will note that after 180 mEq of bicarbonate were administered the serum bicarbonate rose from 5 to 10 mEq per liter. After a further 45 mEq the serum bicarbonate rose from 10 to 28 mEq per liter. My interpretation of these changes is that resumption of normal liver function led to an increased removal of lactate from the blood. If we assume that the lactate was distributed throughout all the cell water, the bicarbonate deficiency was about 1,000 mEq, not 300 mEq. As Dr. Williams emphasized, these patients really need intensive care. I think that often we do not realize the severity of the acidosis. Frequently very few clinical signs of acidemia are evident, and a virtually normal P_{CO_2} is found in the face of an arterial pH of approximately 7.0. This may be related to the insidious onset of the acidosis. The lactic acid may accumulate over a period of several days without the respiratory compensation generally associated with acute metabolic acidosis.

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*Michael N. Berry, M.D., Associate Clinical Professor of Clinical Pathology and Laboratory Medicine.

One word about the etiology of this syndrome. There is considerable evidence that the normal liver can remove lactic acid from blood at rates far in excess of the capacity of other tissues to form it.[10] It follows that prolonged accumulation of lactate in blood indicates a failure of hepatic function. This applies not only to lactic acidosis secondary to shock or to myocardial infarction where the splanchnic circulation is impaired, but also to those cases classified as idiopathic lactic acidosis, many of which have been associated with phenformin intoxication.

Recent work by Mulhausen and coworkers[11] has underlined this relationship. Nearly all of the 91 subjects with cirrhosis studied by these investigators had some degree of hyperlactatemia, and at least ten patients could be classified as having severe lactic acidosis. Thus, although only about 40 percent of patients with idiopathic lactic acidosis have overt liver disease, in the present state of our knowledge it would seem desirable to regard every patient with lactic acidosis as having some disturbance of hepatic function.

Editor's Follow-Up:

After the case had been presented at this conference, a renal biopsy was performed on the patient. Electron microscopic examination demonstrated features consistent with Kimmelstiel-Wilson disease. Because of the possibility that the patient might have Refsum's disease, a specimen of serum was examined for phytanic acid, but none was detected. Following discharge from the hospital he was treated with NPH insulin and diphenylhydantoin. Diabetic control was excellent, myoclonic jerking movements decreased, and his weight gradually increased.

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PRESSURE-REGULATED VENTILATORS PROSCRIBED IN CARDIAC ARREST

"If you are using a ventilator [on a patient in cardiac arrest], you have to use a volume ventilator since the type that is pressure-regulated will be tripped every time you compress the chest, and the patient will end up getting zero ventilation. That's an extremely important point; you cannot use a pressure-sensitive ventilator to ventilate a patient on whom you are doing cardiac compression. It has to be a volume respirator."

—JAMES R. JUDE, M.D., Miami

Extracted from *Audio-Digest Anesthesiology*, Vol. 10, No. 20, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

Usual—Customary—Reasonable

A California Perspective

RALPH C. TEALL, M.D., *Sacramento*
With the Collaboration of Herman H. Stone, M.D., Riverside

AMERICAN PHYSICIANS AND American health care insurance agencies have given wide and enthusiastic acceptance to the idea of a uniformity of fee charges for each defined physician's service for all patients of any individual doctor, and to the idea of a range of such usual fee charges, which reflect those of each community, and which can be used to define the amount to be paid by any insuring agency. These ideas have come to be known as the usual, customary and reasonable basis of paying for physicians' services.

As so often occurs, a brief retrospective review of the origin and background of these terms may be very helpful in clear understanding of their usefulness and significance in contemporary society.

Beginning at least as early as 1945, the California Medical Association has been privileged to receive a series of penetrating studies of problems of medical care insurance. Many of these related to problems that were developing in California Physicians' Service (Blue Shield), and reflected some disharmony between the California Physicians' Service in its developing years and a number of practicing physicians in California.

A fairly direct development sequence in such studies began with a psychological study of the doctor-patient relationship which was submitted in May 1950 to the California Medical Association and the Alameda County Medical Association by Ernest Dichter, Ph. D. Among a great many fundamental observations in that report was the recognition of the great importance of the high cost of medical care to an understanding of the doctor-patient relationship. Dr. Dichter reported that most of the doctors he interviewed admitted readily that, in general, costs were high, but that the general attitude he detected could best be characterized as one of defensiveness. He also noted that the real determinant for a doctor's fee was the doctor's own self-evaluation, which was usually quite high, and that this evaluation of his own work was generally the most real and deep criterion used by the doctor in determining fees.

Dr. Dichter was told that competition dictated the fee to a considerable extent, and that standard fees were determined by customary rates in the area, but he noted that the doctor's own self-evaluation determined whether he felt he must be bound by local customs or might set his own standards. Dr. Dichter concluded that while the problem of costs and fees was a very major one, an important step to its resolution would be accomplished if each physician would charge equal prices to everyone he treated.

The study by Dr. Dichter was extended by a summary and projection of his report, and by some action recommendations, by Mr. Rollen Waterson, who was then the executive secretary of the Alameda-Contra Costa Medical Association, and Mr. William Tobitt, who was then the executive secretary of the Orange County Medical Association. Among many valuable suggestions of this Waterson-Tobitt projection, there occurred the recommendations "that each physician set his own valuation of his services and make available to patients his schedule of fees," and "that the medical association officially condemn the practice of charging those better able to pay more than the value of the services set by the physician and contained in his own schedule of fees."

Significant further development of these themes occurred in the report of a special California Phy-

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Submitted 13 January 1969.
Reprint requests to: 2626 L Street, Sacramento 95816.

sicians' Service Study Committee (chairman: Dr. Wilbur Bailey of Los Angeles) which reported to the California Medical Association House of Delegates in 1952. Among the recommendations of this study committee report were:

> "That each individual physician be urged to accept the principle of individual conformity of fees, and to formulate an individual fee list to which, in the absence of agreement with his patient to do otherwise, he will adhere. . . .
>
> "That each component county medical society of the California Medical Association, or its branches, be urged to formulate and regularly revise a fee list whose basis shall be the average fee charged the average patient by the average physician-in its county. . . .
>
> "That the California Medical Association formulate a state fee list, which shall be a composite of county lists, and which may be adopted by any county as its list in lieu of a locally determined one. The purpose of county and state fee lists shall be to serve as guides to insurors in formulating realistic indemnity schedules."

On this basis, the study committee proposed, and strongly urged, a type of indemnity plan under California Physicians' Service, for which it proposed the term "average fee plan." The committee noted that while this proposal was based on a kind of fee schedule, the term *fee schedule* savored too strongly of the element of compulsory acceptance; the committee suggested that the purpose of the "average fee plan" was to avoid such compulsive conformity, and proposed the term *fee-lists* for the kinds of schedules required.

The term *average* applied to fees, physicians and patients stimulated significant resentment, and to many people the term *fee-list* was not clear. As a result, unfortunately, the study committee report was neither well understood nor well accepted. It was not highly regarded by the then current Board of Trustees of California Physicians' Service, who were deeply distracted by other problems at the time, and the suggestions of the study committee report were not immediately implemented. However, the report was referred to the newly formed Medical Services Commission of the California Medical Association. This committee, under the leadership of Dr. Leslie Magoon, continued a study and review, and prepared a restatement of the proposed "average fee plan." This restatement, entitled *Problems of Medical Care Insurance and the Usual Fee Indemnity Plan, a Restatement,* was submitted to the Council of California Medical Association in May of 1954.

The Medical Services Commission report is an excellent study of insurance fundamentals. Unfortunately, it was never widely publicized to California physicians, nor was it well accepted at the time by the California Medical Association Council or House of Delegates. The report did note that an insured person will have certain "adequate" protection against financial shock only if his insuring agency's indemnity schedule approaches or becomes identical with his physician's fees. However, the individual physician must first set his own fees, and physicians in any community must first establish the level, and relative values, of community fees before any insuring agency can find a way to make its indemnities approach these established fees. The report then explored whether there was any possible compromise to a fixed fee schedule which would allow physicians to control their own individual fees and which could recognize that there are variations in ability among physicians, and variations in difficulty of care among patients, which should be reflected in the fees to be paid. Following the lead of the earlier California Physicians' Service study committee, this Medical Services Commission restatement concluded that a very satisfactory compromise was indeed possible. The restatement substituted the term *usual fee* for *average fee* and re-presented a "usual fee indemnity plan" which it summarized as follows:

> USUAL FEE INDEMNITY PLAN
>
> If a physician charged the same fee for the same service to each of his patients it would be possible to write an indemnity policy, based on these fees, which would give real certainty and adequacy of reimbursement to the patients receiving his services.
>
> Similarly, if each physician charged the same fee for the same service to each of his patients, and if most of the physicians in a community had very similar fees, it should be possible to write an indemnity type insurance contract which would give certain, adequate reimbursement to the patients of this majority group of physicians.
>
> If, on the other hand, a patient sought care from a physician whose individual fee schedule was higher than that of most of the physicians in his community (by reason of unusual skill, experience or prestige), so long as the higher schedule was known to the patient, he would still have certainty of reimbursement to the extent that he would know exactly how much greater his expenses would be than the reimbursement schedule, and he would then knowingly and willingly be accepting less than complete reimbursement from his insurance.
>
> In the same way, any physician anticipating unusual difficulties in the care of a particular case should have the privilege of charging more than his usual fee by reaching an understanding with the patient concerned; after explanation of the unusual problem, before service was given. If there were to be any deviation from the usual fee, the patient should know it in advance.
>
> Briefly, the usual fee indemnity plan proposes that the insuring agency repay to the insured person most

> of what he has spent for medical care. If his physician charges him the usual fee charged by most doctors in his community, the amount repaid will be nearly all he has spent.
>
> This is just what most owners of medical care insurance thought they were going to receive when they bought their insurance.

While concomitant studies were going on elsewhere, it appears that these quoted California studies did introduce, and did most clearly define, the term *usual fee* and the importance of the concept in establishing certainty of insurance coverage while safeguarding freedom of action for both patient and physician.

During the next few years, a considerable amount of continuing exploration of the concept of payment of the "usual" fee of physicians went on, both in California and elsewhere (notably in Wisconsin and Indiana).

The Wisconsin Physicians Service had become interested in the possibility of a full-payment program, with no fee schedules and no income limits. In 1954, Wisconsin Blue Shield offered a major illness program of payment, with deductibles and coinsurance, based on the customary, usual and reasonable charges of the physicians. A "no fee schedule" program was introduced in Racine and Eau Claire counties in 1955, and, as a result of the successful experiment in these areas, was made available throughout Wisconsin in 1957. Payment in full was provided on a physician's charges which were deemed to be customary, usual and reasonable if they did not exceed the general level of charges by other physicians who rendered such services under similar or comparable circumstances within the medical community in which the charge was incurred.

In Indiana a military dependent's medicare program was successfully operated as early as 1956, without any formal fee schedule and with the physician charging his usual fees.

A very significant development for California occurred when the studies of the Riverside County Medical Association, beginning in 1957, convinced the group of physicians embraced in that association that labor wanted certainty of coverage with no income ceiling, and that doctors wanted no fixed fee schedule. In 1959, the Riverside association requested that California Physicians' Service offer a "no income clause" program. Such a program was actually written for one insured group (Food Machinery Corporation) on a pilot basis, and was based on the payment of "usual, customary, and reasonable" fees; and these terms were carefully spelled out and defined in the contract itself. With careful administrative review of claims operations, done by Riverside physicians headed at that time by Dr. Herman Stone, the program was very well received; it soon spread to many other groups in the Riverside area and then to many other areas in California, which experimented with the concept, and with its control by careful continuing administrative review by physicians.

In 1962 a special interim study committee of the California Medical Association House of Delegates, which was then studying the problems of physicians' fees for welfare medical care programs, took another look at the concept of usual, customary or reasonable fees. This committee learned that, from a dictionary or legal standpoint, the terms did not have a separate and distinct meaning. The committee recognized that the definitions proposed by the Riverside County Medical Association, (which had been later adopted almost verbatim by the California Medical Association) did make very important distinctions between the terms usual, customary, and reasonable, but that these distinctions were valid only because they were defined in the contract, rather than because of their intrinsic meaning or general usage.

(As a matter of interest, this interim study committee did itself make a significant error when it recommended that the California Medical Association advise the California State Leigslature that "the payment of physicians for contractual services rendered be based upon what is the usual, customary or reasonable fee for that individual physician." It is obvious, in retrospect, that there is no "customary" fee for an *individual* physician in the light of the original Riverside definitions.)

The terms *usual, customary* and *reasonable* gradually spread across the United States, stimulated by concurrent thought and independent experiment in several areas more or less at the same time. A number of Blue Shield Plans, with a similar objective, introduced the concept of paying physicians' fees on the basis of the "prevailing fee" in the area. The term *prevailing* seemed very similar to the concept of the earlier term *customary*. However, *prevailing* was defined in different ways by different groups; it was found to have no consistent meaning in common usage or in law, and its use appeared to erode the clarity of the terms *usual, customary* and *reasonable.*

Even where the original terms were retained. their meaning became blurred, and for many parts of the United States the phrase "usual and customary" has been widely used in such a way as to make the terms almost synonymous, or interchangeable.

The confusion in terms, and the need for commonly understood definitions, became even more apparent with the development of the United States Federal Medicare Law in 1965. This law authorized payment of physicians' fees on the basis of a "reasonable" charge in whose determination "there shall be taken into consideration the customary charges for similar services generally made by the physician . . . as well as the prevailing charges in the locality for similar services." On careful study of the law, its original intent, and its subsequent administrative interpretation, it became clear that there was really a close similarity in concept, if not in words, between this law and the usual, customary, and reasonable idea and that an equivalence of meaning could be established. Thus, Mr. Howard Hassard, legal counsel for the California Medical Association, as well as for the California Blue Shield and the National Association of Blue Shield Plans, pointed out in March 1966 that *reasonable* in these statutes is defined precisely as in the common law rule, but that the statute uses the term *customary* where the common law uses the word *usual,* and uses the word *prevailing* where the common law uses the word *customary,* but the criteria are identical.

It remained for Mr. Arthur Hess, the administrator of the Federal Medicare Law in its early days, to introduce another clarifying concept, namely that the term *customary* (called *prevailing* under the Medicare law), should refer to those charges which fall within the range of charges *most frequently* and *most widely used* in the locality for particular medical procedures or services. The same administrator suggested that the range of prevailing charges in a locality might well turn out to be different for physicians engaged in a specialty practice than for those who engaged primarily in general practice, and that this might lead to the development of more than one range of such customary or prevailing charges for application by the insurance carrier.

Many very interesting distortions have occurred, and will probably continue to occur in the future, in the use of these terms. For example, an interim study of the California State Legislature proposed that physicians' fees in the California medicaid program (Medi-Cal) be paid on the basis of usual, customary or reasonable, *whichever is least.* The same program, while purporting to follow the "reasonable, customary, and prevailing" concept of the Federal Medicare Law, has grossly distorted this concept by back-dating the level of payment to an experience nearly two years old, with no opportunity for up-dating in response to the general inflationary trend of the entire economy; it has even limited the top of the range of payable fees to the sixtieth percentile of this outdated base. Similar distortions are occurring in many other parts of the United States. (It is to be hoped that the California experience may be corrected at an early date by the adoption, as a basis of payment, of the California Blue Shield physician profile system to determine what is the customary range of usual fees in California communities.)

The value of this usual, customary and reasonable concept is better recognized with each passing day. The inherent opportunity to provide certainty or near certainty of coverage (as in "paid-in-full" contracts), with no income ceiling for the insured, and with no fixed fee schedule for the physician, is producing wide acceptance of the terms and the ideas behind the terms. Their survival and their usefulness, however, depend in very large measure on accurate and commonly understood definition of them, and a uniformity of meaning wherever the terms are used.

At the clinical convention of the American Medical Association in Miami Beach, in December 1968 it was formally recognized, by the House of Delegates, that there is a growing tendency to incorporate the terms *usual, customary* and *reasonable* into national contracts for insurance. It was realized that this required a clear definition of the terms used in any given contract. For this reason, the American Medical Association House of Delegates officially adopted, as guideline definitions for this purpose, a series of definitions very similar to those which had been initiated by the California Physicians' Service in Riverside County in 1958 and had been in use by the California Medical Association since that date. These American Medical Association definitions read as follows:

". . . That the AMA adopt the following definitions and distribute them to all state medical associations for their individual consideration and guidance:

" 'Usual' is defined as the 'usual' fee which is charged for a given service by an individual physician in his personal practice (i.e., his own usual fee); 'Customary' is defined as that range of usual fees charged by physicians of similar training and experience for the same service within a given specific limited geographic or socio-economic area; 'Reasonable' is defined as a fee which meets the above two criteria, or, in the opinion of the responsible local medical association's review committee, is justifiable in the special circumstances of the particular case in question."

The House also resolved that "whenever these terms are used in contracts or laws, they be specifically defined in those documents."

It is increasingly clear that the continuing viability of the *usual, customary* or *reasonable* idea must rest on close adherence by each individual physician to a uniform system of charging the same fee for the same service to each person in his practice. It must also rest on accurate identification by insuring agencies of the actual range of such usual charges in each community, as well as in each specialty, and on the conscientious recognition of factors in the care of any particular patient which may make charges reasonable in particular circumstances which would not be usual for the individual physician or customary for the community.

The actual determination of the range of usual fees which is customary for any particular community, and the circumstances which can make a non-conforming charge reasonable, will require the utmost in understanding, forebearance, and cooperation of peer review committees of physicians in each community. Wide interest, support and participation, of as many physicians as possible in each community, in such peer review activities, is a very vital public service function of the medical profession.

It is clear that the appropriate and optimal use of the *usual, customary* or *reasonable* criteria for payment of physicians' fees offers a very fundamental contribution to resolution of problems of cost, utilization and availability of essential medical care services to the American people, and to strengthening of existing insurance mechanisms throughout the United States.

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DIAGNOSIS OF LIVER INJURIES

"Much has been written about the diagnosis of liver injuries, and there are many available diagnostic criteria. Penetrating wounds by their very presence demand exploration. The once traditional probing is purposeless at best and deceiving at worst. Nor can we confess to any enthusiasm for the injection of radiopaque materials or other time-consuming attempts to demonstrate peritoneal penetration. The latter can easily be determined by a small incision at no risk, if the peritoneum is intact. The incision can be enlarged for further exploration if peritoneal penetration has occurred. Negative explorations are associated with minimal morbidity and mortality. The same can assuredly not be said for failure to explore patients who have sustained serious intraperitoneal damage."

—Rudolf J. Noer, M.D., Louisville, Kentucky
Extracted from *Audio-Digest Surgery,* Vol. 15, No. 21, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

The Physician Profile System

CARL E. ANDERSON, M.D., *Santa Rosa*

■ *The Physician Profile System is currently the most efficient and equitable mechanism of administering the payment to physicians under the usual and customary charge programs. Local peer review must be closely linked with the system to provide the assurance of reasonableness of charges, to resolve differences of opinion, and to scrutinize the utilization of health care resources.*

In actual practice, the Profile System permits for gradually increasing charges, both for the individual physician and for the medical community. It is equally capable of giving effect to lowered charges which sometimes follow technologic improvements.

Usual and customary programs have not proved to be inflationary, and have developed conservative trend patterns which permit realistic prediction of future program costs. Experience has shown that physicians have not abused the usual and customary charge programs. Administrative and peer review devices provide an impressive array of checks and safeguards against abuses in the utilization of benefits and in the payment of physicians' charges.

THE PAYMENT OF sums of money by insurance carriers and prepayment plans to physicians for the services they provide to subscribers or beneficiaries is a rapidly growing activity. The enactment of Public Law 89-97—Medicare—in 1965 produced a sudden massive increase in the volume of carrier payments to physicians and stimulated a broadened interest in the "how and how much" of this process.

A crucial question is: How much is a physician to be paid for a given service? Courts of law have traditionally held that a physician—like any other professional person — is entitled to be paid a *reasonable* charge for his services. One definition of "reasonable" would hold that a charge should be based upon "common usage and acceptance." Expanding upon this concept, Dr. Herman Stone and the Riverside County Medical Society in about 1960 proposed that the terms "usual," "customary" and "reasonable" be used to determine the appropriate or just fee to be paid a physician. These terms were rapidly accepted by the California Medical Association and the American Medical Association. With minor variations, they form the basis for determining "reasonable charges" under the Medicare law.

California Blue Shield is currently paying "reasonable charges" to physicians for services to more than 2.5 million Californians. Other Blue Shield plans and some commercial carriers throughout the nation are paying reasonable charges, "prevailing charges," or are administering "paid in full pro-

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grams" and "no-fee-schedule programs" which embody similar concepts.

Under reasonable charge programs, as administered by California Blue Shield, a physician's charge is paid if it is his *usual* charge for the service and if it is within the *customary range* of charges made by physicians in the same community for the same service, *or* if it is judged to be *reasonable* by *local peer review,* considering all of the medical facts and circumstances.

In order to process tens of thousands of claims daily—and to apply to each of them the test of usual and customary, or reasonable—a rapid, reliable system is essential.

The Physician Profile System is the most modern, most complete and most sophisticated administrative mechanism yet achieved for paying physicians on the basis of usual and customary or reasonable charges. When combined with local peer review on the question of "reasonableness," it would appear to be the most flexible, responsive and just system which could be devised at the present time for the payment of physicians in massive insurance and social programs.

Determination of The "Usual" Charge

Every charge which a physician makes for each service—as indicated by submitted claims—is recorded to his account and stored on the carrier's computer tapes. Over a period of time, it usually becomes apparent that the physician charges one fee for a specific service (RVS code number) more often than he charges any other fee for that service. The fee he charges most frequently is his *usual* fee for that specific service or procedure. For example: Dr. A. did 20 appendectomies in the last six months. He charged $200 for four of these, $250 in 12 cases, and $275 in the remaining four. From this, $250 is his usual fee for an appendectomy, and that is the "usual" that will be used to determine the fee he will be paid until a change occurs in his pattern of charges. If he starts to charge $275 more often than any other charge for appendectomy, $275 will show up within a short time as his most frequent and therefore his *usual* charge for an appendectomy.

A continuous record is kept of all of the charges made by each physician for the services he performs most frequently. The individual physician's *usual* charge for each of the services which make up his "profile" are updated monthly in order to reflect changes which may be taking place in his pattern of charges. (In some Blue Shield Plans physicians are asked to file their usual charges in advance and are permitted to change them at specified intervals, usually once or twice a year.)

Determination of The "Customary Range"

In actual practice in a medical community, the charges made by physicians for a given service tend to cluster about a certain figure which might be statistically identified as the "mode" or the "mean" (average) or the "median" (mid-point). A certain amount of variation above and below the "cluster point" is generally considered to be "normal." This variation reflects differences which might exist in the age, training and experience of the practitioners as well as in overhead and other items concerned with the economics of their practices. On the other hand, charges which exceed by a wide margin those which are commonly made, are considered to be outside the "customary range" and are reduced by the carrier to the "top of the customary range."

The determination of this "top of the range" is the most difficult and most controversial aspect of the system. The statistical methods and terms used to define the "top of the range" as well as their implications are often poorly understood, even among physicians and legislators. The term "percentile" is most often used in this regard and is defined: "That point or value in a serially ordered array of data below which occurs the corresponding percentage of cases."

Thus in the case of the appendectomy, if all the charges made for this operation by all the physicians in the community were laid out in order from the lowest to the highest, the 70th percentile (for example) would be the point—or level of charge below which 70 percent of the charges fall (Table 1).

In the usual and customary programs of California Blue Shield the 90th percentile of charges is used to determine the top of the customary range. Charges which exceed that point are reduced to the 90th percentile, even though they may be the usual charges of the physicians submitting the claims.

This does not mean that the top 10 percent of charges are reduced. As may be seen in the example in Table 1, the 90th percentile is the same as the 93.5th percentile, so that only the highest

6.5 percent of charges (those above the 93.5 percentile) are reduced. In many instances the 90th percentile may coincide with the 95th or even the 100th percentile. In actual application, use of the 90th percentile as the top of the range of customary charges results in reduction of fewer than 5 percent of all charges, and, for any one service, usually results in a reduction for only 2 or 3 percent of physicians.

As in the case of the *usual* charge, the *customary* ranges are constantly updated. Over 2,000 types of services performed by 24,000 physicians in 68 geographic areas of the state are under continual study. Some changes in the customary range criteria occur daily. This provides built-in assurance that the customary range will reflect changes in the charge patterns of the community.

Or Reasonable

When the computer prints out a check for payment of an amount below that which was billed by the physician, it signifies that the charge was above the physician's *usual* charge or above the *customary* range. It does not necessarily indicate that the charge was not reasonable. A patient may present a difficult, complex or unusual problem, requiring more than the usual amount of time, effort or exertion by the physician, thus justifying a charge over and above what might otherwise be paid. The decision as to the reasonableness of a charge in such circumstances is necessarily made by physicians and is a proper subject for local peer review.

Each county and district medical society has a functioning committee of physicians appointed for this purpose. Any physician who believes that his charges have been unfairly reduced, or that circumstances justify an increased fee in certain cases, should avail himself of the advice and assistance of his local peer review committee. The same mechanism is available to carriers and others who feel that physicians are unjustly raising their charges. The carrier usually follows the decision of the local review committee.

In some instances, not all parties may agree with the decisions of the local review committee. In California, an appeals mechanism has been established at the state level by the California Medical Association. Rules of procedure to assure "due process" have been developed by legal counsel for the guidance of local and state review committees. Final recourse may be had to the courts of law.

Questions and Problems

As the Physician Profile System has been implemented in different areas of the country, sometimes the first reactions have been antagonistic, expressions revealing apparent confusion at the seeming complexity of the system. But on further experience these reactions usually give way to surprise that it is really very simple.

Once the actual workings of the system are understood, there remain a number of important questions relating to the influence of the Physician Profile System on the level of fees and the costs of medical care. Some of these questions and their answers are contained in a recent Special Supplement of *The Blue Shield.* The following two questions and answers are direct quotes:

"Don't usual and customary programs tend to inflate physicians' charges?

"There is no evidence that these programs are inflationary over the long term. There has been some evidence that charges have increased in the early stages of some of the programs. This is largely attributable to their having caused some physicians to examine their fees for the first time in years."

"Won't usual and customary coverage lead to fee schedules?

"No. It is specifically designed not to influence fees. The question does raise two possibilities. The first is that the Plan may fail to keep charge levels current. Physicians have adequate defenses against this through agreements between the Plan and the Medical Society or through participating in both.

"The second possibility is that a significant percentage of physicians will respond to usual and customary coverage by seeking the maximum possible payments. If this happened it would destroy the checks and balances inherent in normal fee ranges. In theory this is possible. Physicians can destroy any prepayment mechanism. In practice, Blue Shield's experience is that if physicians are permitted to set fair fees, they will preserve the integrity of the process."

Administrators and others concerned with the financing of such programs as Workmen's Compensation insurance, which have traditionally used fixed fee schedules, have expressed the additional concern that usual and customary fees do not permit accurate prediction of program costs. This concern is unwarranted, as is shown by experience gained in usual and customary fee programs in

California, indicating a very consistent and predictable gradual increase in physicians' charges of approximately 4 percent per year. This rate of increase tends to confirm the findings of the *Physician Fee Index* published by the Bureau of Research and Planning of the California Medical Association since 1963. This study reports an annual rate of increase of 4.3 percent over a five-year period. The existence of such reliable trend figures makes realistic actuarial projections of program costs quite feasible.

Not Used for Medi-Cal

Although California's Medi-Cal law, implementing Title XIX of the Social Security Act, requires the payment of "reasonable charges" based upon "customary and prevailing" charges, the Physician Profile System cannot now be used in administering this program. In September 1967, the State Health and Welfare Agency imposed a regulation prohibiting the payment to physicians of fees in excess of the 60th percentile of charges being made on 1 January 1967.

The effect of this regulation, still operative, is to require reduction of the charges for the majority of services performed by the majority of physicians serving the program. A Profile System operating under such a restrictive fee ceiling would be entirely meaningless—like a baseball game played on a handball court. The Physician Profile System is largely self-regulating. The imposition of rigid external fiscal controls entirely negates its values and effectiveness.

Fiscal Stability and Consumer Protection

Among the many misconceptions about usual and customary charge programs is the erroneous belief that no restraint is exercised and no ceiling is placed upon the fees a physician may be paid. Nothing is further from the truth. There is a series of checks and restraints upon unusually high fees and unreasonable inflation and also upon the inappropriate and wasteful utilization of services.

In addition to the limiting factors inherent in the usual charge and in the top of the customary range, there are other factors and procedures which serve as protection against abuses.

Usual fees and customary ranges *may go down as well as up.* Technical advances from time to time make it easier to perform certain procedures, and charges then may be reduced. A recent example resulted from the effect of automated laboratory procedures on the charges for certain blood chemistry determinations. The Profile System promptly reflects such lowering of charges.

Local peer review involves much more than passing upon the reasonableness of a disputed fee. In many local medical societies panels of physicians personally inspect, on a rotating basis, up to 20 percent of all the claims submitted by local physicians, and must approve not only the fees charged but also the propriety of the services rendered. Physicians found habitually to "overcharge," or to "overprescribe" or in other ways to practice medicine which is not up to accepted community standards are subject to disciplinary procedures ranging from reprimand or recommendation of fee reduction to recommendations for legal action in cases of suspected fraud, or even to revocation of license. Utilization and fee review are conducted by consultants and advisors in the offices of carriers as well as at the local level.

A final check on unreasonable fees and inappropriate utilization lies within the legal responsibility of the carrier. As a contractor in governmental programs, the carrier has the legal obligation to pay only "reasonable" charges for "covered" services. In standard, non-governmental programs, the carrier has a moral as well as a legal obligation to protect and conserve the subscriber's premium dollars. Carriers that permit payments to escalate unreasonably or that are lax in their scrutiny of utilization are risking loss of subscribers and cancellation of governmental contracts.

TABLE 1.—*Determination of Percentile*

In a given county, during January 1969, 400 appendectomies were performed. The charges made by the operating physicians ranged from $180 to $350. The charges were distributed as follows:

Charge Per Case	*Number of Cases*	*% of Total No. of Cases*	*Cumulative % of Total No. of Cases (Percentile)*
$180	1	0.25	0.25
$200	100	25.00	25.25
$225	99	24.75	50.00
$240	125	31.25	81.25
$280	49	12.25	93.50
$300	24	6.00	99.50
$325	1	0.25	99.75
$350	1	0.25	100.00

In the above example, the 50th percentile of charges would be at $225. The 60th, 70th and 80th percentiles would all be $240, the 90th percentile would be at $280.

California
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EDITORIAL

Management of Psychomotor (Temporal Lobe) Seizures

THE TERM "psychomotor epilepsy" was introduced in 1937 to designate a heterogenous group of seizures which did not conform to the classical descriptions of grand mal, focal or petit mal seizures. This has proved useful in emphasizing to the physician that the term "petit mal" should be reserved only for a characteristic disorder which develops in childhood or adolescence (onset rare, if ever, after the age of 20), with highly specific clinical features. Petit mal attacks are characterized by transient clouding of consciousness, an absence, lasting usually 5 to 30 seconds, with or without minor movements of the head or extremities (myoclonic jerks), following which the patient is alert and continues his usual activity. Occasionally loss of of postural tone may occur, and the youngster may drop to the floor in an akinetic petit mal attack. Often the child is unaware of having an attack and it may be dismissed by parents as momentary daydreaming or inattentiveness. The delineation of psychomotor attacks from petit mal has important implications with regard to the etiology of the seizure, the correlation with focal brain pathology, the need for diagnostic completeness, and the choice of therapy. Whereas petit mal seizures have not been associated with any focal pathology in the brain and pathophysiologically are considered to originate probably in deep central structures in the region of the thalamus, psychomotor seizures are a special form of focal seizure originating in either temporal lobe. Hence the term "Temporal Lobe Seizure" is widely used as a synonymous term. Recently, the term "limbic lobe" epilepsy has been used to also indicate that the disorder involves structures apart from the temporal lobe, although the limbic system has important projections to that lobe. (The limbic system is that phylogenetically old portion of the brain that serves as an anatomical and physiological basis for the emotions.)

The clinical features of temporal lobe epilepsy have been well-summarized by Walter in this issue of CALIFORNIA MEDICINE. These may be, on occasion, bizarre to the point of being considered hysterical or psychotic symptoms. The episodes last longer than petit mal attacks and are usually followed by post-seizure amnesia. One may note purposeful motor activity and behavior that is incongruous for the immediate situation. Movements noted may include lip smacking, fumbling with clothes or even disrobing. In addition to such automatisms, perceptual disorders, illusions, and "forced thinking" are common. Clinical patterns are highly variable but generally stereotyped in a given patient. Diagnosis is dependent upon the history obtained from the patient and of equal importance are the observations of family or friend to describe the behavior during the attack. The nature of the aura and of the behavior following the attack must be sought. Diagnostic errors commonly occur when the physician cannot obtain and clarify the history from an observer other than the patient.

The occurrence of a seizure disorder in a child or adult may have major consequences upon their general behavior apart from the seizure disorder itself. The behavioral problems vary considerably, but are most likely to occur in patients with frequent psychomotor attacks. A tendency toward easy excitability, irritability, aggressive behavior, and "schizophrenic reactions" has been commonly noted. Similarly, depressive reactions are also common. Some of these appear to derive from difficulties in social and occupational adjustments. The intensity of the behavioral problems commonly makes evaluation of the severity and frequency of the seizures difficult to ascertain. The emotional consequences of the attacks may be more disabling than the seizure disorder itself. Patients, and their families, must be educated concerning the nature of the disorder, and, at times, formal psychotherapy is an essential adjunct to drug therapy.

Falconer and Taylor (Arch. Neurol. 19, 353, 1968) have reviewed the pathologic findings in 100 cases of surgically treated cases of temporal lobe epilepsy, 53 percent of which had "medial temporal sclerosis" or other scarring, 22 percent had small cryptic tumors, and only 25 percent revealed no structural lesion. Thus, the occurrence of small angiomas or gliomas must be considered in the diagnosis, particularly with the onset of the seizure disorder after the age of 20. A detailed neurological examination should always include a careful plotting of the visual fields to detect small lesions in the temporal lobe. Routine skull films are essential in detecting the occasional occurrence of a calcified lesion in the temporal lobe. While electroencephalography has contributed greatly to the delineation of these cases, the presence of a normal electroencephalogram need not detract from the diagnosis in a patient with a characteristic history. The occurrence of an elevation in the cerebrospinal fluid protein is generally indicative of a neoplastic or other space-taking lesion in the temporal lobe and usually warrants radiologic contrast studies.

The key to the successful management of such patients is the ability of the physician to prevent the occurrence of seizures with drugs. Diphenylhydantoin and phenobarbital, in combination, are most useful in the management of psychomotor seizures. Primidone (Mysoline®) and a wide variety of other anti-grand mal drugs play a supplementary role. Specific anti-petit mal drugs, which include ethosuximide (Zarontin®) or trimethadione (Tridione®) are not indicated. The most common error in the treatment of such patients is the failure to use enough medication. Diphenylhydantoin and phenobarbital should be increased to the point of tolerance in an effort to control the seizure disorder. If drug dosages are gradually increased in time, frequently the depressant effects of the medication may be minimized despite high dosages. Diphenylhydantoin is slowly excreted from the body and need never be given more than twice a day. When diphenylhydantoin is begun, at 300 or 400 mg daily, about five days are required to obtain satisfactory blood and tissue levels. Thus, the "Dilantinizing" dose is approximately 1,500 mg.

Factors responsible for the failure of drug therapy include (1) improper classification of seizure type and with failure to use appropriate drugs, (2) failure to administer an adequate dosage, (3) the frequent shifting of drugs and premature withdrawal of drugs, (4) poor education of the patient with regard to his illness and the need to take medication, and (5) the lack of recognition of social and economic needs of the patients. Perhaps the single most common cause for poor control of seizures is the failure of the patient to take the prescribed dosage! The monitoring of the blood diphenylhydantoin level with periodic laboratory tests has been demonstrated to result in improved control, because this supervision induces many patients to greater conscientiousness in taking the amount prescribed. The absence of nystagmus in a patient presumed to be taking large amounts of diphenylhydantoin and phenobarbital should suggest to the physician that the patient is not taking the designated dosage. When an anticonvulsant or a combination of anticonvulsants give indications of being effective, the medications should be maintained. The pressures from the patient and others to utilize newer drugs should be reserved for those resistant or allergic to therapy with adequate dosages of well-established compounds.

Drug therapy is less successful in controlling psychomotor seizures than the other seizure disorders and, in appropriately selected patients, surgical therapy is indicated. Criteria for surgery include: (1) psychomotor seizures of sufficient frequency that the patient is incapacitated socioeconomically; (2) intensive drug therapy has been unsuccessful; (3) availability of facilities for detailed clinical and electrophysiological analysis essential for neurosurgical exploration. Surgical excision is of value in a limited number of patients with epilepsy and search must be continued for newer drugs, without serious toxicity, to reduce our current failures in drug therapy.

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Phenformin and Lactic Acidosis

SINCE THE EARLIEST days of its clinical use in the treatment of diabetes, there has been published concern about the possible role of phenformin in the causation of lactic acidosis.[1] Elsewhere in this issue of CALIFORNIA MEDICINE is the twenty-seventh published case report of lactic acidosis occurring in a diabetic known to have been treated with phenformin. We are aware of reports of 63 diabetic patients with lactic acidosis, of which 54 cases have been published and the remaining nine cases are unpublished,[2,3,4] known to us in our own experience. Of this number, 38 were receiving phenformin at the time they developed lactic acidosis, five patients were known to have been taking tolbutamide, two chlorpropamide and six insulin.

This very high incidence of use of phenformin among reported and known cases of lactic acidosis in the diabetic leads naturally to the question of cause and effect. Since lactic acidosis is known to have occurred both in diabetic patients who were taking no drug therapy and in diabetics on therapy other than phenformin, the relationship is not clear. On the other hand one of the more convincing observations is the fact that at least ten of the reported cases of lactic acidosis in which phenformin was being taken occurred in patients who were taking no other medication and who were previously in metabolic balance and who had no other identifiable cause for the lactic acidosis.

The subject of lactic acidosis has been reviewed in detail elsewhere.[2] The accumulation of quantities of lactic acid sufficient to create severe and life-threatening metabolic acidosis is a very common event in patients who are in shock from a variety of causes, including hemorrhage, myocardial infarction and septicemia. A significant association with gram-negative infection has been noted. A few patients, however, have been demonstrated to develop lactic acidosis apparently spontaneously, and in the absence of other recognizable disease. It is noteworthy that among reported diabetic patients who have developed "spontaneous" lactic acidosis, in whom there was not identifiable additional cause for lactic acidosis, all were receiving phenformin.

The latter factor we believe to be of major significance, since virtually every other case of lactic acidosis in the diabetic has been preceded by an acute illness whose characteristics are such as to be related to lactic acidosis in the non-diabetic as well. In other words, in at least ten diabetics who developed lactic acidosis there was no other identifiable cause than phenformin ingestion. One case of attempted suicide by ingestion of 1,500 mg of phenformin did not result in an elevation of blood lactate[5]; while a second case of ingestion of 850 mg resulted in an unidentified metabolic acidosis.[6] Furthermore, it seems clear that many thousands of patients have taken phenformin as therapy for diabetes mellitus and have not developed lactic acidosis.

Part of the confusion in our ability to assign a direct relationship of phenformin ingestion to an incidence of lactic acidosis lies in our incomplete knowledge of the mechanism of action of this drug. Recent evidence that phenformin is rapidly metabolized, probably by the liver, to para-hydroxyphenethylbiguanide casts much doubt upon the results of *in vitro* examinations of the mechanism of action of the drug.[7] Furthermore, there is a significant relationship between the *in vitro* effects of phenformin and its concentration in experimental situations. Evidence exists which supports the idea that normally achieved blood levels of phenformin are not capable of producing the metabolic effects which have been directly associated with the increased production of lactic acid by tissues exposed to phenformin. These effects are, however, possible with higher concentrations of phenformin, and such levels have only been demonstrated in diabetics who develop lactic acidosis while taking phenformin.[8]

In the absence of definitive evidence, however, it is essential to have a rational approach to the use of this drug in the therapy of the diabetic. In this context, we would point to the following information:

1. Apparently spontaneous lactic acidosis, with frequent fatal termination, has occurred in diabetic patients being treated with phenformin alone, in whom there was no evidence of other potential cause of lactic acidosis.

2. Among therapeutic agents being given to diabetic patients who have developed a catastrophic illness which led to lactic acidosis, there is a greater association with the use of phenformin than with any other therapeutic agent, by a very wide margin.

3. *In vivo* human studies exist which validate the existence of elevated resting blood lactate in patients receiving phenformin and which indicate that lactic acid is produced in increased amounts by diabetic patients given phenformin acutely.[8,9]

4. Phenformin is metabolized by the liver and excreted in the urine. Seventeen of 18 reported cases of lactic acidosis in patients taking phenformin, in whom estimates of renal function are available, show evidence of impaired renal function at the onset of their lactic acidosis.

5. Three patients with lactic acidosis, who had been receiving phenformin were shown to have elevated levels of blood phenformin in concentration capable of inducing increased lactate production by tissues in *in vitro* experiments.[8]

For these reasons, and until unequivocal evidence can be presented to the contrary, we are of the opinion that there is a relationship between the incidence of lactic acidosis and the use of phenformin in the treatment of diabetes mellitus. It would appear that the hazard is greatest among patients who have impaired renal function and those who are subjected to other causes of lactic acidosis, such as severe gram-negative infection or acute myocardial infarction. We therefore recommend that reemphasis be given to the current instructions packaged with this drug to the effect that phenformin is contraindicated in patients who have impaired renal function, and in the presence of other significant acute illness, chronic infection, and acute or chronic heart disease.

It should be pointed out that a significant number of patients who developed lactic acidosis while on phenformin had the onset of lactic acidosis accompanied by nausea and vomiting and abdominal pain. The occurrence of these symptoms in any diabetic taking phenformin should lead to the immediate discontinuation of the drug and careful observation of the patient for metabolic acidosis.

Therapy of lactic acidosis remains empirical. Therapeutic modalities reported to date include the correction of the metabolic acidosis with the use of large amounts of sodium bicarbonate intravenously, peritoneal dialysis, methylene blue, glucose and insulin, and tromethamene (THAM®). Additionally it is agreed that measures designed to maintain intravascular volume, tissue oxygenation, cardiac function and control of infection are important in the management of this condition. Experience indicates that correction of the acidosis with intravenous sodium bicarbonate, along with detailed attention to the correction of identifiable defects in hydration, hemoglobin levels, cardiac function, tissue oxygenation and control of infection are the most significant contributors to survival of these patients. The other therapeutic modalities (methylene blue, THAM, glucose and insulin) await further confirmation.

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A Physician Is Worthy of His Hire

A WORKMAN IS worthy of his hire. This has long been an important tenet of our national philosophy. Our society today also holds that discrimination is an evil thing. Whenever discrimination is suspected or exposed, there is apt to be a great public outcry accompanied by demands that the situation be corrected. Government and the courts are generally sympathetic to those who are victims of discrimination.

But in certain quarters, physicians are thought of as being somehow different. The same government and the same labor unions who stand steadfastly against the payment of anything less than prevailing wages in every *other* aspect of health care services, apparently have chosen to make a special case of physicians' fees. By various devices they persistently seek to reduce or to curtail the fees paid for services rendered by physicians, perhaps in the forlorn hope that by this means they will somehow be able to control the skyrocketing costs of medical care. A case in point is the current limitation of payments to the "60th percentile" in the Medi-Cal program. Another is the recent "freeze" on Medicare Part B payments until 1970. The result of these attitudes and efforts is not only discriminatory against essential members of the health care team, but more importantly, it should not be overlooked that since in the long run one gets about what one pays for, sooner or later this will lessen the quality of the services received by the beneficiaries.

The problem is complex. The need to be able to predict costs to a reasonable degree is essential to sound financing, whether a program be governmental or in the private sector, but the laborer is also worthy of his hire. Physicians, like attorneys, who also render personal professional services, feel that as individuals they have some right to place a value upon the work they have performed, a value which may be quite different in different circumstances. Yet it is only right that this value bear some relationship to what others would charge for similar services in similar circumstances. To many, mostly outside the profession, standardized fee schedules seem to be the only answer. Fixed salaries for physicians appeals to others, and again those others are mostly outside the profession. The former approach would tend to standardize the level of care more or less at the level of the standardized fee, which experience shows is more often low than high. The latter causes the physician to be working for someone other than the patient and to this extent may lessen his sense of responsibility to an individual patient. Neither particularly encourages excellence or rewards service above and beyond the ordinary. Most physicians believe that in the long run individual fee for service best serves the patient and that it tends to promote better medical practice. However, there must be reasonable restraint and reasonable control.

Organized medicine in California has played a leading role in what appear to be increasingly successful efforts to find means to provide for flexibility, predictability and reasonable control of abuse in the charges physicians make for professional services with minimal interference with traditional individual fee for service rendered. Two reports elsewhere in this issue of CALIFORNIA MEDICINE (pages 337 and 342) recount important progress. The related concepts of "usual," "customary," and "reasonable" which have been developed and refined by the California Medical Association were adopted by the American Medical Association last Fall. And recently California Blue Shield has introduced a new "Physician Profile System" which applies the earlier concepts in what appears to be practical fashion.

This progress is significant in that it should make possible the reconcilement of traditional individual fee for service with acknowledged necessity for reasonable predictability and control of abuse in the aggregate of physicians' charges. The machinery is now available to avoid the discrimination which is now all too prevalent. Let's have some more fair play in the matter of physicians' fees. The physician like any other workman is worthy of his hire.

On Polluting the Biosphere

WE ARE JUST beginning to sense the enormity of man's capability to inflict discomfort and even destruction upon himself and his descendants through pollution of planet Earth and its atmosphere. It is awesome to hear it said that DDT, a chemical introduced by man on a wide scale less than three decades ago, can now be detected in any sample of water drawn from any ocean in any part of the world. Solid wastes have also begun to accumulate alarmingly. With respect to the atmosphere, Starkman elsewhere in this issue of CALIFORNIA MEDICINE (page 309) notes that emissions from automotive vehicles are largely responsible for the formulation of photochemical smog, and that during the next decade no significant reduction in total air pollution is likely to be achieved. It is clearly evident that the time is approaching, and approaching rapidly when we must realize that the human nest is in fact a closed ecological system. Its pollution poses the greatest peril not only to present but to future generations of mankind.

If life is to persist indefinitely within any closed system some means must be found to convert useless or toxic wastes into needed resources. Wastes which are not converted can only accumulate until they become physically or chemically deleterious to the system and finally destructive to the life within it. It appears that for the first time in history man's technology has developed to the point where it is producing wastes of quantity and character which are beyond the capability of this biosphere to convert back into needed resources.

It seems quite clear that mankind has come to the threshold of an entirely new era in its history. Henceforth, the health and well-being of the species will increasingly depend upon the biological wisdom and behavioral restraint of each generation with respect to cumulative pollution of this biosphere. Dramatic instances of space travel notwithstanding, mankind as a whole is unlikely to escape the confines of this terrestrial nest. Surely this portends new and heavy responsibilities for scholars and practitioners in many fields of human biology and health care. It is not too early for the medical profession to become concerned and involved. In fact this profession should begin to play a leading role.

"FEELING" PRECORDIAL MOVEMENTS AT THE APEX

"In general, there are three types of [precordial] movements at the apex [during systole] which one can appreciate with his hand or can record with the graphic method. One of these is a normal movement. Second is a so-called hyperdynamic movement, which is an exaggeration of the normal; one sees this in mitral regurgitation and in thyrotoxicosis and other types of overactive movements which are qualitatively somewhat similar to normals. A third type is a so-called sustained outward movement, which is appreciated by the hand as a sustained outward thrust. This is seen in ventricular hypertrophy of various types; and variants of it are seen in ventricular aneurysm, in idiopathic hypertrophic subaortic stenosis, and in enlarged dilated failing ventricles. . . .

"Sometimes one feels over the precordium during systole not an outward thrust but rather an inward movement, and this may be very deceptive. Some years ago, people described this particular situation as a diastolic heart beat and have found that it is characteristic of constrictive pericarditis."

—ERNEST CRAIGE, M.D., Chapel Hill, North Carolina
Extracted from *Audio-Digest Internal Medicine,* Vol. 15, No. 22, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

LETTERS *to the Editor*

More On Rh Immunization

To the Editor: There were three communications in the February issue of CALIFORNIA MEDICINE* about the prevention of Rh immunization through the use of anti-Rh immune globulin, which cover the subject completely. A few additional points must be made, however, in order to avoid misinterpretation of the letter from Dr. Hattersley.

In his opening paragraph, he states that 1 ml (300 micrograms) of the anti-Rh gamma globulin concentrate "given intramuscularly to an Rh— woman within 72 hours after she delivers an Rh+ child almost invariably prevents primary immunization to the Rh factor." This statement is supported by a rapidly enlarging bibliography, including the article by Jennings et al in the same February issue of CALIFORNIA MEDICINE. Rarely has any trial therapy on human subjects been so highly successful, so safe, and so easily executed. As the figures from the Ortho Research Foundation show,[1] more than 2,500 Rh— unsensitized women were injected within 72 hours of the birth of an Rh+ infant and were completely protected, except for two understandable failures, whereas more than 1,000 similarly exposed and unprotected women had an incidence of almost 7 percent Rh sensitization. By now, probably over 200,000 women in this country and several times this number in Canada and Europe have been so treated, with equally good results.

On the basis of such striking evidence, there can be little doubt that every unsensitized Rh— woman delivered of an Rh+ infant should be offered this protection.

The indications for the use of the anti-Rh immune globulin are perfectly clear. Even giving it unnecessarily to a woman with an ABO-incompatible infant would do no harm. Although ABO incompatibility between mother and child, e.g., Group O Rh— mother vs. Group A Rh+ child, does tend to protect against Rh sensitization, this is not absolutely so and occasional sensitizations do occur even in such cases. Stern and coworkers showed[2] that injections of A Rh+ cells into O Rh— individuals did primarily sensitize 5 out of 32 subjects. Clarke has shown[3] that 4 percent of ABO and Rh incompatible pregnancies have more than 0.25 ml of fetal red cells in the maternal circulation after delivery, and that a considerable number of maternal sensitizations have resulted in such cases. The original trial (using RhoGAM®) in more than 30 medical centers in this country excluded the ABO incompatible pregnancies because of the lower risk and the scarcity of material. There is no reason, however, for not using the concentrate when it is abundant and commercially available, to protect the Group O Rh— woman who might become sensitized in rare cases by her Group A Rh+ baby.

As to the recommended injection of 1 ml, containing 300 micrograms of anti-Rh immune globulin, this has been proved to prevent immunization in more than 99 percent of cases. The only failures have been: a rare instance where the woman was "sensitive" to the gamma globulin as the result of numerous large doses given for protection against hepatitis and developed a large local reaction, probably not permitting absorption of the injected material; half a dozen other women who either received the injection too late (beyond 72 hours) or had a relatively large "bleed" from the fetus and did not receive enough anti-Rh antibody to neutralize all the fetal cells.

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*Jennings, E. R. et al: Prevention of Rh hemolytic disease of the newborn, Calif. Med., 110:130-134, Feb. 1969.

Hattersley, Paul G.: Anti-Rh immune globulin—How should we use it? (Letter to Editor), Calif. Med., 110:176-177, Feb. 1969.

Diamond, Louis K.: Erythroblastosis fetalis—Now a preventable disease (Editorial), Calif. Med., 110:170-172, Feb. 1969.

Obviously, even such a perfect therapeutic measure should not be used thoughtlessly nor in a fixed dose. Individualization of each case and observation of the newborn infant will permit the careful physician to prescribe a larger dose when indicated. As much as 5 ml of concentrate can be given if the infant is anemic at birth and therefore may have bled into the mother; this possibility can be readily detected by doing a fetal cell count on the mother's blood. Very little additional research and observation are needed to clarify these minor problems which may affect 2 percent or less of the women at risk. It is obviously not too soon for anti-Rh immune globulin to be used regularly in the appropriate manner to protect unsensitized Rh— women from Rh immunization and thereby wipe out hemolytic disease of the newborn due to Rh incompatibility. As our legal friends might say: Caveat medicus.

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Secondary Syphilis Diagnosed As Mononucleosis

To the Editor: I read with interest the case report "Secondary Syphilis Misdiagnosed as Infectious Mononucleosis" by Marcus A. Conant, M.D. and Barton Lane, M.D. in the December, 1968 issue of California Medicine (pages 462-464). There are several points in the report that I feel warrant comment.

First, I was somewhat dismayed that three physicians saw the patient and diagnosed infectious mononucleosis without the benefit of readily available laboratory studies that could have been helpful in confirming or refuting the clinical impression.

In the paragraph concerning the treatment of the secondary syphilis, the authors indicated that they attempted to elicit a Herxheimer reaction by giving 300,000 units of crystalline penicillin G in 2 percent aluminum monosterate (PAM) on the first visit. Although severe consequences of this reaction are usually associated with late syphilis, potentially severe reactions can occur in early syphilis and would be better avoided especially in an outpatient.

In the concluding paragraph of the article, the authors point out the difficulty in the differential diagnosis of early syphilis with atypical manifestations.

A VDRL would certainly be indicated to help rule out the entities mentioned. In addition, a concurrent specific treponemal antigen test would further help to exclude the occasional biological false positive (BFP) reaction that these conditions can produce and thereby hasten diagnosis and treatment.

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Usual, Customary And Reasonable

To the Editor: We appreciate being advised of your plans to publish a "California Perspective" of the *usual, customary and reasonable* concept of fee charges.

The State Medical Society of Wisconsin, through its Health Insurance Division, Wisconsin Physicians Service-Blue Shield, first offered a "Reasonable Charges" program in the sale of a major illness expense benefit in 1954. Since this still fell short of providing "full payment" for most of the people in Wisconsin, the next step was a countywide enrollment in Racine County in 1955. This enrollment rapidly expanded into other areas of the state and involved the full use of customary, usual and reasonable charges for all benefits included in the contract, such as surgery, in-hospital medical care, anesthesia, radiology and the like. The fee schedule was eliminated as such and Blue Shield paid the physicians' charges so long as they were usual, customary and reasonable within the medical community in which the services were rendered.

By 1957, Wisconsin Physicians Service had ceased the sale of scheduled contracts and offered only "usual, customary and reasonable" coverage with a maximum of $1,000 or $10,000 of benefits per illness at the option of the purchaser.

This program began as a means of meeting the ever-changing demands of the people for full payment of the physician's bill. It was our answer to constantly revising the fee schedule and income limits to meet changing economic conditions and the need for insurance devices that would keep up with medical advances.

We look back now and say we are proud to have been there at the beginning.

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Rh Nomenclature

To the Editor: In his review of my book[1] in your Journal of September 1968 (Calif. Med., 109:269, Sept. 1968), Dr. Perkins has stated that I have "sided with Alexander Wiener in the latter's campaign to restrict Rh nomenclature to the Wiener terminology." This suggestion of a partisan motive to me and introduction of politics into a scientific field cannot be allowed to pass without comment.

I would like Dr. Perkins to know that I was using the Fisher-Race nomenclature myself. When I made a careful study of the problem of Rh nomenclature prior to writing my handbook, I became fully convinced that the original Rh-Hr nomenclature was simple, logical and scientifically superior to the Fisher-Race nomenclature. It was then, and only then, that I abandoned the use of the C-D-E terminology.

I have found that most workers who follow the Fisher-Race terminology lack the will to study the problem objectively and decide for themselves. Not only that, even some well-known blood group serologists in England and elsewhere who, though personally convinced of the superiority of the Rh-Hr nomenclature, still cling for reasons best known to themselves, to the other nomenclature. Each one seems to ask, "Why should I bell the cat?"

In the meantime, many funny things are being taught and written. Can anything be more absurd than to state[2] that an imaginary antibody, anti-d, causes 63 percent positive reactions with the red cells of Caucasians, while admitting at the same time in a footnote that the antibody is "not yet discovered."

The followers of the dual system of Rh nomenclature can hardly be blamed and the responsibility for the 20-year-old chronic controversy must rest with the Division of Biologics Standards of the National Institutes of Health which, having initiated the controversy, continues to take no active steps to rectify its own error. A time may come—and soon—when the NIH may find itself forced to modify its stand and rationalize Rh nomenclature. The simple fact must be remembered that for a nomenclature to be called "international" it must be a single nomenclature and superior to all others.

Meanwhile, advocates of the correct Rh nomenclature should perhaps be prepared to be dubbed as campaigners to restrict Rh nomenclature to the Wiener terminology. I don't mind.

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Information

Management of Pulmonary Insufficiency

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Material Supplied by the California Heart Association

PULMONARY INSUFFICIENCY occurs acutely or chronically under conditions which generally include in whole or in part signs of breathlessness, obstruction of airways and retention of secretions. Institution of proper therapy calls for a prompt integration of the history, physical examination and laboratory tests.

The features of most historic significance are concerned with sputum and wheezing. For example, it is difficult to make a diagnosis of chronic bronchitis without eliciting a history of sputum production on arising in the morning. A yellow or greenish color to sputum often signifies acute bronchopulmonary infection. Sudden cessation or marked reduction of sputum volume in a patient chronically bringing up sputum may indicate retained secretions or mucoid impaction. Gradual reduction of sputum volume over months or years accompanied by dyspnea may signal the development of pulmonary emphysema. Wheezing is associated with bronchial asthma or bronchitis; it also occurs in severe congestive heart failure. Swelling of the ankles may be the result of cor pulmonale or mechanical obstruction of the inferior vena cava by depressed diaphragms. Smoking habits, occupation background and exposure to noxious gases, fumes, or dusts are helpful in establishing an etiologic diagnosis.

The decision to employ a specific means of mechanical aid to ventilation is most dependent upon the sensorium of the patient. Conservative measures are preferred when the patient is mentally alert regardless of the disturbances in arterial blood gases. The breathing pattern is important in establishing whether reassurance, intermittent positive pressure breathing with bronchodilators or intubation are indicated. Short gasping inspirations in patients with obstructive airway disease may be caused by an anxiety reaction or acute bronchopulmonary infection. Prolongation of expiration occurs in bronchospasm and in emphysema. Occasionally, the sole sign of airway obstruction is vigorous contraction of the abdominal rectus muscles during expiration. Ausculation of the chest for wheezes, rales and audibility of breath sounds is helpful in the differential diagnosis of bronchospasm, congestion, fibrosis, pneumonitis and pneumothorax. A tracheal wheeze may result from the tracheobronchial collapse due to emphysema or to upper airway obstruction.

Analysis of the arterial blood gases is a mandatory part of the clinical examination in every patient with pulmonary insufficiency (for detailed description of arterial blood gas interpretations see Sackner, *Medical Times* 95:79, 1967). Important measurements obtained from the arterial blood analysis include pH, carbon dioxide tension (pCO_2), base excess, oxygen tension (pO_2) and oxygen saturation. The blood pH is normally fixed between 7.38 and 7.42. It is affected by a change in pCO_2 and an accumulation of non-volatile acids or bases. Arterial pCO_2 ranges from 38-42 mm Hg and is inversely proportional to alveolar ventilation. Base excess is normally zero; a positive value indicates a base excess or a non-volatile acid deficit, a negative value indicates a base deficit or a non-volatile acid excess. The base excess can theoretically be determined by titration with a strong acid to a pH of 7.40 at a pCO_2 of 40 mm Hg and a temperature of 38° centigrade. In practice, base excess is determined indirectly by calculation from a nomogram using values for pH, pCO_2 and hemoglobin concentration. The base excess should be considered as the indicator of metabolic and the pCO_2 that of respiratory disturbances. A blood pH below 7.38 indicates acidosis. If the pCO_2 is greater than 42 mm Hg a respiratory acidosis exists whereas if the base excess is less than —3 (i.e. —4, —5, —6 etc.) a metabolic acidosis is present. A positive base excess (+3 or greater) associated with a respiratory acidosis generally indicates that in whole or part the respiratory acidosis has been chronic.

The usual arterial blood gas disorders in pulmonary insufficiency involve hypoxemia and respiratory alkalosis or acidosis. Respiratory alkalosis and hypoxemia are often found in the early stages of status asthmaticus and in atelectasis. Many patients with obstructive airway disease have hypoxemia only. Chronic respiratory acidosis is usually seen in patients with chronic bronchitis alone or

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Chief, Division of Pulmonary Disease, Mt. Sinai Hospital, Miami Beach, Florida.

as the predominant disease in combined bronchitis and emphysema. Acute respiratory acidosis may occur in patients with preexisting pulmonary diseases who have superimposed infections, retained secretions, narcotic dosage or overdosage, congestive heart failure, status asthmaticus or pneumothorax. Metabolic acidosis may complicate acute respiratory acidosis in conditions such as status asthmaticus and pulmonary edema.

A chest roentgenogram should always be obtained in patients with pulmonary emphysema who develop acute pulmonary insufficiency. In these patients, pneumothorax and pneumonitis may give few or no physical signs. An electrocardiogram should be obtained routinely since cardiac arrhythmias are frequent. A gram stain of the sputum smear should be examined immediately to help in the choice of an antibiotic.

In terms of management, we have found the following classification of pulmonary insufficiency useful. It is based on (1) the state of the sensorium, (2) obstructive airway signs, (3) signs of retained secretions and (4) acid-base balance as estimated by arterial blood gas analysis.

Alert; Obstructive Airway Signs; No CO_2 Retention. This is probably the commonest type of pulmonary insufficiency. It is found in status asthmaticus and in anxiety reactions in patients with preexisting pulmonary diseases. Hypoxemia and respiratory alkalosis are generally present. Psychotherapy is by far the most important mode of treatment. The physician must repeatedly assure the patient that breathlessness will decrease if respirations are slowed and if he relaxes. The physician must remain in the patient's presence and give vocal encouragement until this is accomplished. In addition, but not as a substitute, intermittent positive pressure breathing using slow respiratory flow rates and nebulizing 4-8 drops of racemic epinephrine in 5ml IV aminophyllin solution for 15 minutes every 3 hours may be useful. If psychotherapy is ineffective, sedation must be employed using mild tranquilizers to narcotics as indicated. Intravenous steroid and aminophyllin therapy are often beneficial. If there is coexisting metabolic acidosis as in status asthmaticus, initially 1 ampule of $NaHCO_3$ (44.5 mEq) should be given for every —4 to —5 mEq of base excess and further requirements followed by serial arterial blood gas determinations.

Alert; Obstructive Airway Signs; Acute Respiratory Acidosis. This condition develops in certain patients with status asthmaticus, in patients with emphysema and/or chronic bronchitis who develop a bronchopulmonary infection or anxiety reaction. These patients frequently show rapid shallow respirations and hold their chests in a high inspiratory position. Reassurance should be employed but is not as effective as in those patients without CO_2 retention. These patients should be treated with intermittent positive pressure breathing until arterial pCO_2 returns to normal. If bronchospasm exists, intravenous steroids and aminophyllin should be employed. Narcotics and sedation are usually contraindicated because of their depressant effects on the respiratory center. However, if the tachypnea persists and if intermittent positive pressure breathing is fought by the patient, then a trial of sedation may be indicated. This type of treatment should only be utilized if the patient is in an intensive care unit under close medical surveillance and if intubation equipment is immediately available with close monitoring of arterial blood gases. Base deficits should be corrected with intravenous sodium bicarbonate.

Alert; Retained Secretions; No CO_2 Retention. Representative examples in this category include pneumonitis, post-operative atelectasis and acute exacerbations of chronic bronchitis or bronchiectasis. The best results in terms of removal of secretions are obtained with chest physiotherapy. A trained chest physiotherapist performs shaking and clapping of the chest and postural drainage, and educates the patient in correct coughing. Nasotracheal suction should always be done initially by an experienced attending physician before turning this task over to nursing since it is often difficult to carry out properly. Deep breathing exercises and intermittent positive pressure breathing should be used in atelectasis. Heated aerosol is indicated for loosening secretions in large airways, the ultrasonic nebulizer for small airways. Antibiotics should be administered if the sputum is purulent. Provided the patient remains alert, bronchoscopy is usually not required.

Alert; Obstructive Airway Signs; Chronic Respiratory Acidosis. Patients with chronic bronchitis and/or emphysema may show this condition. The blood pH is near normal, pCO_2 and base excess elevated and hypoxemia is present. If arterial pCO_2 is less than 62 mm Hg with near normal pH, these patients should be maintained on intermittent positive pressure breathing four times a day, or as necessary, at home or in the hospital. Arterial pCO_2 above 62 mm Hg represents an unstable condition; the patient may become acutely acidotic with minimal stresses. These patients should be hospitalized and given hourly or two hourly treatments with intermittent positive pressure breathing until pCO_2 falls below 62 mm Hg. Measures must be taken to keep pH normal by correcting the coexisting compensating metabolic alkalosis with saline, ammonium chloride, potassium chloride, arginine hydrochloride or diamox as dictated by cardiac, renal and electrolyte considerations. The goal in therapy is to keep pCO_2 below 62 mm Hg while keeping blood pH normal during room air breathing; it is not to bring pCO_2 down to a normal value of 40 mm Hg. It is important to ventilate these patients with oxygen concentrations not greater than 30 percent because respiratory center depression may occur immediately after a treatment with the respirator if higher oxygen concentrations are used. As in other patients with obstructive airway signs intravenous steroids and aminophyllin, chest physiotherapy and nasotracheal suction are useful adjuncts. This group of patients also frequently has incipient grades of congestive heart failure. Digitalis and diuretic therapy added to regimen occasionally bring pCO_2 to normal and partially relieve the hypoxemia.

Stupor; Acute Respiratory Acidosis. This condition is most likely to occur in patients with obstructive airway disease who have been given sedation, or develop an acute bronchopulmonary infection or have incomplete elimination or anesthetics or neuromuscular agents following surgery. These patients should be treated with continuous intermittent positive pressure breathing until pCO_2 returns to normal. A volume limited respirator with a mask is preferred since leaks can be overcome by increasing the volume delivered by the machine, whereas pressure limited respirators do not cycle well if inflation pressures greater than 25 cm water need to be employed. If the latter occurs and a volume limited respirator is unavailable, then intubation with a cuffed endotracheal tube should be carried out. Bedside bronchoscopy is useful. Tracheostomy should be considered if there are copious secretions and if the patient cannot be taken off the endotracheal tube after 96 hours. Since gastric ileus occurs in many of these cases, the gastric contents should be emptied by a nasogastric tube.

Stupor; Obstructive Airway Signs; Acute and Chronic Respiratory Acidosis. These patients are best treated by continuous controlled ventilation by a mask using a volume-limited respirator. This can also be handled with a pressure limited respirator but one must be prepared to do more frequent monitoring of arterial blood gases and ventilation. However, intubation is usually necessary when the latter type of respirator is employed. The goal of therapy is to reach a normal pH over a 6-24 hour period, not a normal pCO_2. Rapid correction of arterial pCO_2 to normal levels with alkaline pH in these patients is associated with a fatal encephalopathy. Adjunctive therapy includes chloride replacement or bicarbonate diuresis, antibiotics, nasogastric suction and diuretics. If secretions are thick and copious and a tracheostomy employed, lung lavage should be done every 4 hours with a 5 ml solution of equal parts of intravenous $NaHCO_3$ solution and saline.

Coma; Respiratory Acidosis. These patients should be bronchoscoped at the bedside, secretions removed and a cuffed endotracheal tube inserted. They should be placed on continuous controlled ventilation with a volume limited respirator. The goal of therapy is restoration of normal pH. Depending upon the base excess, replacement of chloride or bicarbonate should be carried out. Nasogastric suction, antibiotics, diuretics and tracheostomy are useful adjunctive measures.

California Medical Association

Council Highlights

Highlights of the Actions of the California Medical Association Council Meetings, January 10 to 11, Los Angeles, and February 14 to 15, Los Angeles

This summary is published so that CMA membership may be advised in brief of the actions of the Association's Council. It covers only major actions and is not intended as a detailed report. Full minutes of these meeings are available upon any member's request to the CMA office.

549th Meeting, January 10 to 11, 1969, Los Angeles

Recommendations for improvement in the Medi-Cal program were approved. They cover benefits, control of over-utilization and abuse, fee-for-service and reimbursement, financing and cost control, and administration of the Medi-Cal program.

Guidelines for components of an adequate program of health care (voluntary health insurance) coverage were approved. The guidelines are the essential elements to be included in policies or contracts offered to the public, and they will help to assure the availability, accessibility and provision of good medical care.

Steps to combat air pollution were approved. Among the many resolutions was one that "urges the support of studies and enactment of laws which will assure a healthy air supply in the future."

A recommendation urging better liaison by county medical societies with interns, residents, and medical school faculty was approved. This could be accomplished, Councilors believe, through dinners, special county society committees or medical executives.

County medical societies were urged by Councilors, in a resolution which they approved, to estab-

ALBERT G. MILLER, M.D. . . . . President
RALPH W. BURNETT, M.D., Bakersfield . . . President-Elect
WILLIAM F. QUINN, M.D. . . . . Speaker
JOSEPH F. BOYLE, M.D. . . . . Vice-Speaker
RICHARD S. WILBUR, M.D. . . . Chairman of the Council
HAROLD KAY, M.D. . . . . Vice-Chairman of the Council
HELEN B. WEYRAUCH, M.D. . . . . Secretary
MALCOLM S. M. WATTS, M.D. . . . . Editor
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RICHARD W. LEMOS . . . . Sacramento Office
1127 11th St., Sacramento 95814 • 916 444-5532

lish liaison with medical schools so that formal presentations on activities of organized medicine can be made within the medical school. The recommendation was made by the ad hoc Committee on Monterey Workshop.

Resolution expressing appreciation of the work performed by Dr. Charlotte C. Baer, chief medical advisor for California Blue Shield in the Medi-Cal Program, was approved. The resolution, introduced by the San Francisco Medical Society, lauds Dr. Baer for her work with patients, San Francisco physicians "and actually all physicians in California." (She resigned on March 1.)

Establishment of a liaison committee between CMA Council and the State Board of Medical Examiners was approved. Committee members are: John G. Morrison, M.D., San Leandro, chairman; Lewis T. Bullock, M.D., Los Angeles; Frank A. Rogers, M.D., Whittier; Carl E. Anderson, M.D., Santa Rosa; Walter Hopps, M.D., Los Angeles, and Malcolm S. M. Watts, M.D., San Francisco.

Reaffirmation of Council position that Councilors attend board meetings of county medical societies in their districts was voted.

550th Meeting, February 14 to 15, 1969, Los Angeles

A resolution calling for CMA to urge the passage of a bond issue for construction of medical and health facilities at several University of California campuses was approved for submission to 1969 House of Delegates. The resolution stated that CMA "urge the University of California, the governor, the legislature and the people of California to introduce, support and pass a bond issue for capital construction needs for medical and health science education at the several campuses of the University of California as soon as possible."

Guidelines for component medical societies in dealing with complaints of the public were adopted by Council. Recommended guidelines for medical societies are:

- Develop methods of regularly informing the public that there are grievance (or other appropriate) committees to resolve complaints on fees, utilization, and quality of medical care provided by a physician.
- Adopt formal, written procedures and policies, with special forms to record and process complaints, notify complainants about disposition of their cases.
- Review complaints — regardless of their nature — and recognize that "those which involve utilization factors and quality of medical care are as important as elements for resolution as are those which deal with the nature of professional charges."
- Accept complaints from all sources, whether from the patient or his private or public representative.
- Use existing committees or establish a special committee to review a sample of claims, either before or after they have been processed for payment by various insurance and prepayment organizations.

CMA position on nearly 60 bills in the state legislature was approved by Council. An analysis of each bill, with recommended position, was submitted earlier to Councilors by the CMA Legislative Committee. Four bills on "Measure of Damages," approved by the Legislative Committee and ratified by Council, cover revisionary trust; pain and suffering; commission on personal injury awards, and termination of liability.

A recommendation to include continuing medical education as a principle for relicensure was referred to the House of Delegates by the Council.

A study by CMA and Department of Professional and Vocational Standards of the proposal to establish an Allied Health Bureau was approved by Councilors. Primary purpose of setting up a bureau would be to simplify problems of licensure and certification.

A total of $2,500 for CMA participation in a pilot project on the concept of patient arbitration was approved. The study is being made jointly by the California Hospital Association, the California Medical Association and the American Arbitration Association in ten Los Angeles County hospitals.

Under the proposed program, a new paragraph would be added to the regular hospital admission form stating that the patient agrees to subject any dispute with the hospital to arbitration under the rules of the American Arbitration Association and special rules of the California Hospital Association. Medical staff members may also join the arbitration agreement.

Recommendations concerning medical staff activities were approved by Councilors. They include the following:

- Leave the decision to individual medical staffs as to whether podiatrists should be accepted for staff membership.
- Issue standing orders to hospital personnel to perform heroic resuscitation unless the physician indicates otherwise; each medical staff adopt its own method, preferably in writing, to indicate that a patient is not to receive heroic resuscitation.

A schedule for completion of the 1969 California *Relative Value Studies* was approved. The new *RVS* will be distributed to Councilors in April and considered at the May Council meeting.

In Memoriam

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

Barclay, Gordon Roy, San Gabriel. Died 9 February 1969 in San Marino of heart disease, aged 46. Graduate of University of Toronto Faculty of Medicine, Canada, 1945. Licensed in California in 1947. Doctor Barclay was a member of the Los Angeles County Medical Association.

⁂

Bashor, Ernest G., Los Angeles. Died 1 March 1969 in Los Angeles of cardiovascular disease, bronchopneumonia, aged 77. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1915. Licensed in California in 1915. M.D. degree from California College of Medicine, 1962. Doctor Bashor was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

⁂

Cullum, George Wilson, Marina Del Rey. Died 25 November 1968, aged 45. Graduate of Medical College of South Carolina, Charleston, 1947. Licensed in California in 1955. Doctor Wilson was a member of the Santa Clara County Medical Society.

⁂

Dailey, Warren F., Anaheim. Died 8 March 1969 in San Luis Obispo, aged 44. Graduate of Kansas City College of Osteopathy and Surgery, Kansas City, Mo., 1955. Licensed in California in 1956. M.D. degree from California College of Medicine, 1962. Doctor Dailey was a member of the Orange County Medical Association.

⁂

Dockendorff, William Orin, Chowchilla. Died 1 February 1969 in Chowchilla, aged 53. Graduate of University of Oregon Medical School, Portland, 1941. Licensed in California in 1942. Doctor Dockendorff was a member of the Fresno County Medical Society.

⁂

Douthat, Robert C., San Diego. Died 20 February 1969 in San Diego, aged 64. Graduate of University of Arkansas School of Medicine, Little Rock, 1930. Licensed in California in 1949. Doctor Douthat was a retired member of the San Diego County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

Dudley, Arthur Oliver, Pasadena. Died 13 February 1969 in Pasadena of coronary artery disease, aged 61. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1931. Licensed in California in 1931. M.D. degree from California College of Medicine, 1962. Doctor Dudley was a member of the Los Angeles County Medical Association.

⁂

Du Puis, Ernest Moise R., Crockett. Died 16 December 1968 in Richmond of pulmonary edema, aged 40. Graduate of Chicago College of Osteopathy, 1954. M.D. degree from California College of Medicine, 1962. Licensed in California in 1962. Doctor Du Puis was a member of the Alameda-Contra Costa Medical Association.

⁂

Eaton, J. Lloyd, Oakland. Died 22 December 1968, aged 66. Graduate of University of California Medical School, Berkeley-San Francisco, 1928. Licensed in California in 1928. Doctor Eaton was a member of the Alameda-Contra Costa Medical Association.

⁂

Gianotti, Ernest Furst, San Francisco. Died 3 November 1968 of cancer, aged 72. Graduate of St. Louis University School of Medicine, 1920. Licensed in California in 1930. Doctor Gianotti was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

⁂

Gunderson, Clayton B., Bakersfield. Died 16 February 1969 in Bakersfield, aged 62. Graduate of Northwestern University Medical School, Chicago, 1935. Licensed in California in 1952. Doctor Gunderson was a member of the Kern County Medical Society.

⁂

Jones, Gertrude Flint, San Francisco. Died 24 February 1969 in Berkeley of cancer, aged 70. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1923. Licensed in California in 1923. Doctor Jones was an honorary and retired member of the San Francisco Medical Society, a retired member of the California Medical Association, and an associate member of the American Medical Association.

⁂

Kehoe, Julius M., Redding. Died 1 February 1969 in Redding of coronary infarction, aged 69. Graduate of University of Michigan Medical School, Ann Arbor, 1931. Licensed in California in 1937. Doctor Kehoe was a member of the Shasta-Trinity County Medical Society.

⁂

Kiskadden, William S., Beverly Hills. Died 15 February 1969 in Los Angeles of myocardial infarction, aged 74. Graduate of University of California Medical School, Berkeley-San Francisco, 1922. Licensed in California in 1922. Doctor Kiskadden was a retired member of the

Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✣

Lawrence, Lester B., Oakland. Died 12 February 1969 in Oakland of myocardial infarction, aged 63. Graduate of University of California Medical School, Berkeley-San Francisco, 1932. Licensed in California in 1932. Doctor Lawrence was a member of the Alameda-Contra Costa Medical Association.

✣

Lecky, Jim Hence, Downey. Died 5 February 1969 in Los Angeles, aged 53. Graduate of Vanderbilt University School of Medicine, Memphis, 1943. Licensed in California in 1951. Doctor Lecky was a member of the Los Angeles County Medical Association.

✣

Leggitt, Clarence Melvon, Long Beach. Died 7 February 1969 in Lynwood of carcinoma of the pancreas, aged 62. Graduate of College of Medical Evangelists, Loma Linda-Los Angeles, 1932. Licensed in California in 1932. Doctor Leggitt was a member of the Los Angeles County Medical Association.

✣

Loewe, Gilbert Martin, Woodside. Died 19 February 1969 in Woodside, aged 80. Graduate of the University of Illinois College of Medicine, Chicago, 1912. Licensed in California in 1954. Doctor Loewe was an associate member of the San Francisco Medical Society.

✣

McCloy, Neil Patrick, San Francisco. Died 27 February 1969 in San Francisco of emphysema, aged 56. Graduate of University of Southern California School of Medicine, Los Angeles, 1938. Licensed in California in 1938. Doctor McCloy was a member of the San Francisco Medical Society.

✣

Moore, Carl Louis, Bakersfield. Died 9 February 1969 in Los Angeles, aged 64. Graduate of University of Pittsburgh School of Medicine, Pennsylvania, 1932. Licensed in California in 1935. Doctor Moore was a member of the Kern County Medical Society.

✣

Rosner, Ben, Belmont. Died 8 February 1969 in San Mateo, aged 48. Graduate of the University of Rochester School of Medicine and Dentistry, New York, 1944. Licensed in California in 1952. Doctor Rosner was a member of the San Mateo County Medical Society.

✣

Scott, Fred Leroy, Riverside. Died 9 February 1969 in Loma Linda, aged 76. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1924. Licensed in California in 1924. Doctor Scott was a member of the Los Angeles County Medical Association.

✣

Shefoff, Henri Alexis, Oakland. Died 1 March 1969 in Oakland of cardiac failure, aged 60. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1935. Licensed in California in 1935. Doctor Shefoff was a member of the Alameda-Contra Costa Medical Association.

✣

Volse, Louis A., Newhall. Died 18 February 1969 in Saugus of myocardial infarction, aged 73. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1925. Licensed in California in 1925. M.D. degree from California College of Medicine, 1962. Doctor Volse was a member of the Los Angeles County Medical Association.

✣

Willems, Leonard Carmody, Glendale. Died 7 February 1969 in Glendale of cardiac failure, aged 71. Graduate of the University of Kansas School of Medicine, Lawrence-Kansas City, 1922. Licensed in California in 1932. Doctor Willems was a member of the Los Angeles County Medical Association.

✣

Wolpe, Leon Zacharias, Los Angeles. Died 4 February 1969 in Los Angeles of coronary occlusion, aged 61. Graduate of Rush Medical College, Chicago, 1933. Licensed in California in 1933. Doctor Wolpe was a member of the Los Angeles County Medical Association.

PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H.
Director, State Department of Public Health

Therapeutic Abortions—Second Annual Report

California's Therapeutic Abortion Act, which took effect 8 November 1967, provides that abortions may be performed in hospitals accredited by the Joint Commission on Accreditation of Hospitals when a committee of the hospital's medical staff finds that there is a substantial risk that the continuance of the pregnancy would gravely impair the physical or mental health of the mother, or that the pregnancy resulted from rape or incest. Applications based on alleged rape or incest must be reported to the district attorney of the county in which the alleged violation occurred. If he does not give an opinion of probable cause of the pregnancy within five days, the hospital's committee may make the decision.

In a separate resolution, the Legislature requested that the State Department of Public Health submit an annual report regarding the experience under the law. The first annual report was summarized in California Medicine, Vol. 108, No. 5, May 1968. The recently issued second annual report presents information on California's first 11 months under the Act, from 8 November 1967 to 30 September 1968.

To evaluate the effect of the law on the childbearing experience of California women, therapeutic abortion figures should be related to the total number of pregnancies in the state. This number is not known because many illegal abortions take place in California, with estimates ranging from 20,000 to 120,000 per year. Without valid pregnancy data, therapeutic abortions must be related to live birth statistics.

During the 11-month period covered by the second annual report, 221 of the state's 477 accredited hospitals received abortion requests. There was a total of 4,291 applications; 3,673 requests (86 percent) were based on danger to the mental health of the mother, 253 (6 percent) on danger to physical health, and 365 (9 percent) on rape or incest.

Three thousand nine hundred and three requests (91 percent) were approved and 3,775 (88 percent) were carried out. Abortions were performed on 89.2 percent of the applicants giving reasons of mental health, 82.6 percent of those whose request was based on physical health and 79.5 percent of those who gave rape or incest as a reason.

The San Francisco Bay Statistical Area (San Francisco, Sonoma, Napa, Solano, Contra Costa, San Mateo, Marin, Alameda and Santa Clara counties), which has 23 percent of the state's births, had 63 percent of the abortions. The Los Angeles Metropolitan Area (Los Angeles and Orange counties) with 44 percent of the state's births had only 19 percent of the abortions. In the San Francisco Bay Area, 31 abortions were performed per 1,000 live births; in the Los Angeles Metropolitan Area, only five per 1,000.

Although these differences cannot be explained without more information and a more intensive analysis of data from several sources, impediments to the applications of the law in Southern California may account for the smaller number of legal abortions there.

Forty of the 77 county hospitals are accredited and 9.6 percent of the abortions were performed in them, although they received a proportionate number of applications (12 percent). The rate of approval in county hospitals (71 percent) was much below that in non-county hospitals (90 percent).

What kinds of women requested and received abortions? Ninety percent were white, a proportion corresponding to the race distribution of live births in 1967. Over half were married. Almost all were California residents. They ranged in age from 12 to 46 years, with a median age of 25. The under-20's had most of the abortions that were performed because of rape or incest. Relative to total live births, women in the age group 15 to 19 and in the over 39 age group had proportionately more abortions than those in the 20 to 39 group.

First pregnancies made up about one-third of the live births and one-half of the therapeutic abortions, indicating there is an over-representation of childless women seeking abortions. The proportion of women with three or more previous pregnancies was equally represented, comprising one fifth of the live births and one-fifth of the abortions.

The effect of the California therapeutic abortion law might be better understood if statistical and epidemiological resources were augmented to permit study of the incidence of illegal abortion and also an assessment of community knowledge and attitudes regarding the law and its application.

REMOVING COMMON DUCT STONES RETAINED AFTER OPERATION

"Ten to 20 percent of common duct operations in which stones are found are second procedures. In other words, the second operation, while not frequent, is not uncommon. Re-operation for the overlooked or retained stone is primarily a matter of getting an overlooked stone out or, less frequently, of doing some additinal surgical procedure in the hope that the stone or stones will subsequently pass if they are unremovable at the time of the first operation.

"Numerous devices and techniques have been described. In one, the blunt end of a catheter is inserted and suction is applied to the other end; in another, a large catheter is put in (almost occluding the common duct), 40 or 50 ml of saline or Ringer's solution is injected, and the catheter is withdrawn. This sometimes seems to distend the duct and allow the stones to come out. A third method is to knead or massage the liver; this will sometimes dislodge stones."

—NORMAN M. CHRISTENSEN, M.D., Eureka
Extracted from *Audio-Digest Surgery,* Vol. 15, No. 20, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

EDUCATION NOTICES

Meetings and Courses

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of the dates of continuing education programs and the meetings of various medical organizations in California is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102; or phone: (415) 776-9400, extension 241.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Postgraduate Course Information

CMA:	**California Medical Association** For information contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. (415) 776-9400, ext. 241.
LLU:	**Loma Linda University** For information contact: John E. Peterson, M.D., Associate Dean for Research Affairs, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.
PMC:	**Pacific Medical Center** For information contact: Arthur Selzer, M.D., Chairman, Education Committee, Pacific Medical Center, Clay and Webster Streets, San Francisco 94115. (415) 931-8000.
STAN:	**Stanford University** For information contact: Thomas A. Gonda, M.D., Associate Dean, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5940.
UCD:	**University of California, Davis** For information contact: Charles J. Tupper, M.D., Dean, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0333.
UCI:	**University of California — California College of Medicine, Irvine** For information contact: Robert Combs, M.D., Associate Dean, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.
UCLA:	**University of California, Los Angeles** For information contact: Donald Brayton, M.D., Associate Dean and Head, Continuing Education in Medicine and the Health Sciences, 15-39 Rehabilitation Center, UCLA Center for the Health Sciences, Los Angeles 90024. (213) 825-6514.
UCSD:	**University of California, San Diego** For information contact: Clifford Grobstein, Ph.D., Dean, University of California, San Diego, School of Medicine, La Jolla 92038. (714) 453-2000.
UCSF:	**University of California, San Francisco** For information contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, Health Sciences, University of California Medical Center, San Francisco 94122. (415) 666-1692.
USC:	**University of Southern California** For information contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 225-1511, ext. 203.

CONTINUOUSLY

Basic Home Course in Electrocardiography. One year postgraduate series, ECG interpretation by mail. Physicians may register at any time. $100 (52 issues). Contact: USC.

GRAND ROUNDS

Medicine

Tuesdays

Medical Grand Rounds: UCLA. 9-10:30 a.m., Assembly Hall, Harbor General Hospital, Torrance.

Wednesdays

Grand Rounds in Internal Medicine: UCSF. 10:30-12:00 noon.

USC Department of Medicine Grand Rounds. 11:00 a.m., Room 1645, Los Angeles County-USC Medical Center.

UCI Grand Rounds in Medicine. 12:30 p.m., Auditorium, School of Nursing, Orange County Medical Center.

Grand Rounds in Internal Medicine. 1:30-3:00 p.m., Fresno General Hospital.

Thursdays

Medical Grand Rounds, UCLA. 10:30-12:00 noon, Room C3-105, UCLA Medical Center.

Fridays

Medical Grand Rounds—CRMP Area IV. 8:00 a.m., Courtroom, Third Floor, Kern County General Hospital, Bakersfield.

Medical Grand Rounds—CRMP Area IV. 8:30 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

Infectious Disease Grand Rounds—USC. 10:00 a.m., Auditorium, Children's Division Building, Los Angeles County-USC Medical Center, Los Angeles.

Medical Grand Rounds—CRMP Area IV. 1st and 3rd Fridays, 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles.

Medical Grand Rounds — CRMP Area IV. 2-3:00 p.m., Classroom, Third Floor, Fresno General Hospital.

Pediatrics

Tuesdays

UCLA. 8:30-9:30 a.m., Sixth Floor Conference Room, Harbor General Hospital, Torrance.

USC. 8:30 a.m., Auditorium, Children's Division Building, Los Angeles County-USC Medical Center, Los Angeles.

CRMP Area IV. 8:30 a.m., Conference Room, Sixth Floor, Harbor General Hospital, Torrance.

CRMP Area IV. 8:30 a.m., Room 4-A, Kern County General Hospital, Bakersfield.

Wednesdays

UCI. 8-9:00 a.m., Held alternately at Auditorium, Orange County Medical Center and the Auditorium, Childrens Hospital of Orange County.

Thursdays

UCSF. 8:30-10:00 a.m., Room 664, Science Building, UCSF.

Cedars of Lebanon Hospital. 8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital.

Fridays

CRMP Area IV. 8:00 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA.

Surgery

Wednesdays

CRMP Area IV. 7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield.

CRMP Area IV. 1st and 3rd Wednesdays. 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles.

Fridays

UCI. 1-2:00 p.m., Auditorium, Orange County Medical Center, Orange.

Saturdays

CRMP Area IV. 9:00 a.m., Room 73-105, Health Sciences Center, UCLA.

CRMP Area IV. 8:30 a.m., Assembly Room, Harbor General Hospital, Torrance.

MAY

May 2-3—**SAN JOAQUIN VALLEY COUNTIES—Regional Postgraduate Institute.** Sponsored by CMA, University of California, Irvine and San Joaquin Valley Counties Medical Societies. Friday-Saturday. 14 hours. $20. Contact: CMA.

May 2-4—**Northern California Chapter, Western Orthopedic Association.** Del Monte Lodge, Pebble Beach. Friday-Sunday. Contact: Mrs. Ida Ruth Haggerty, Executive Secretary, 3901 Ardley Avenue, Oakland 94602. (415) 533-6790.

May 3—**Current Trends in Dermatology.** PMC. Saturday.

May 3—**Self-Expansion: A Critical Appraisal.** UCSF. Saturday.

May 3-4—**Inhalation Therapy.** UCLA. Saturday-Sunday. $40.

May 3-4—**Explorations in Group Therapy.** UCSF at Modesto Irrigation District Auditorium, Modesto. Saturday-Sunday.

May 5-8—**Aerospace Medical Association.** Hilton Hotel, San Francisco. Monday-Thursday. Contact: William J. Kennard, M.D., Executive Vice President, Washington National Airport, Washington, D.C. 20001.

May 5-8—**Civil Aviation Medical Association.** Hilton Hotel, San Francisco. Monday-Thursday. Contact: Charles K. Holbrook, M.D., Secretary-Treasurer, 9901 Diamond Drive, St. Louis 63137.

May 7—**Annual Meeting, Los Angeles County Heart Association.** Hilton Hotel, Los Angeles. Wednesday. Contact: Los Angeles County Heart Association, 2405 West Eighth Street, Los Angeles 90057.

May 7 — **Third Annual Seminar, "The Person Past Fifty."** Santa Teresita Hospital, Duarte. Wednesday, 2:00 p.m. $10. Contact: Bertram J. Kaufmann, Jr., M.D., Chairman, 25 N. Santa Anita Avenue, Arcadia 91006.

May 7-9—**American Association of Genitourinary Surgeons.** Del Monte Lodge, Pebble Beach. Wednesday-Friday. Contact: Harry M. Spence, M.D., Executive Secretary, 4105 Live Oak Street, Dallas 75221.

May 8—**Pediatrics Lecture.** Sponsored by Los Angeles Pediatrics Society in Los Angeles. Thursday. Contact: Mrs. Eve Black, Executive Secretary, P.O. Box 2022, Inglewood 90305.

May 8-10—**Advances in Pediatrics.** UCSF. Thursday-Saturday. $75.

May 8-10—**Association of University Radiologists.** UC Medical Center, San Francisco. Thursday-Saturday. Contact: Harry Z. Mellins, M.D., Department of Radiology, State University of New York, Brooklyn 10021.

May 9-10—**REDWOOD REGIONAL CONFERENCE.** Sponsored by CMA, UCLA and North Coast Counties Medical Societies at Konocti Harbor Inn, Clear Lake. Friday-Saturday. 14 hours. $20. Contact: CMA.

May 9-10—**Effective Medical Writing.** UCLA School of Medicine Extension Division in cooperation with the Southern California Chapter of the American Medical Writers Association. Ambassador Hotel, Los Angeles. Friday-Saturday. Contact: UCLA.

May 9-11—**Annual Meeting, San Francisco Neurosurgical Society.** Del Monte Lodge, Pebble Beach. Friday-Sunday. Contact: Burton L. Wise, M.D., Room U-120, UC Medical Center, San Francisco 94122. (415) 666-1677.

May 9-11—**Principles of Intensive Cardiopulmonary Care.** PMC. Friday-Sunday.

May 10—**Valley Presbyterian Hospital Seminar: New Frontiers in Aging.** Valley Presbyterian Hospital at Universal Sheraton Hotel, Universal City. Saturday.

May 12-15—**American Urological Association.** Hilton Hotel, San Francisco. Monday-Thursday. Contact: William P. Didusch, Executive Secretary, 1120 North Charles Street, Baltimore 20201.

May 12-17—**American Association on Mental Deficiency.** Sheraton-Palace Hotel, San Francisco. Monday-Saturday. Contact: John J. Noone, Ed.D., Executive Secretary, 5201 Connecticut Avenue, N.W., Washington, D.C. 20015.

May 13—**A Day in Therapeutics.** USC at Los Angeles Hilton Hotel. Tuesday.

May 14-15—**Pediatric Symposium.** USC. Wednesday-Thursday.

May 15-17—**Ear, Nose, Throat.** UCSF. Thursday-Saturday.

May 16—**Office Ophthalmology.** USC at Los Angeles Hilton Hotel. Friday.

May 16—**Scientific Session, Annual Physician Symposium.** Council on Clinical Cardiology—American Heart Association and San Francisco County Heart Association. Jack Tar Hotel, San Francisco. Friday. $10. Contact: San Francisco County Heart Association, 259 Geary 94102.

May 16-17—**Pediatric Ophthalmology.** UCLA. Friday-Saturday.

May 17—**Application of Casts, Splints and Bandages.** UCLA. Saturday.

May 17—**Annual Seminar and Barbecue.** General Hospital of Ventura County. Saturday. Contact: Gerald K. Ridge, M.D., 3291 Loma Vista Road, Ventura.

May 21—**East Meets West.** Agnews State Hospital, San Jose. Wednesday. Contact: J. Elizabeth Jeffress, M.D., Chief of Professional Education, Agnews State Hospital, San Jose 95114.

May 23—**What's New in Medicine (UC Alumni Day).** San Francisco. Friday. Contact: UCSF.

May 23-24—**14th Annual OB/GYN Symposium.** Southern California Permanente Medical Group. Beverly

Hilton Hotel, Los Angeles. Friday-Saturday. Contact: Mrs. Shirley Gach, 4900 Sunset Boulevard, Room 3007, Los Angeles 90027.

May 23-24—**Conference on Training of Orthopaedic Assistants.** PMC. Friday-Saturday.

May 23-25—**Frontiers in Medicine.** UCSF and Humboldt-Del Norte Medical Society in Eureka. Friday-Sunday. Contact: UCSF.

May 23-25 — **Roentgen Diagnosis of Diseases of the Heart.** UCLA at the Century Plaza Hotel. Friday-Sunday.

May 24-25—**Computers in Medicine.** UCSF. Friday-Sunday.

May 24-25—**Love, Sex, Marriage.** UCSF at Mendocino State Hospital, Talmage. Saturday-Sunday.

May 24-25 — **Depression — Recognition and Management.** UCLA. Saturday-Sunday. $15.

May 24-25—**Behavior Problems of Adolescence: Organic or Functional.** UCSF at De Witt State Hospital, Auburn. Saturday-Sunday.

May 28-29—**Cancer Symposium.** USC at Los Angeles Hilton Hotel. Wednesday-Thursday.

JUNE

June 2-5 — **Southwestern Surgical Congress.** Sahara Tahoe Hotel, Lake Tahoe. Monday-Thursday. Contact: Jack A. Barney, M.D., 301 Pasteur Bldg., Oklahoma City, 73103.

June 4-5 — **Sports Medicine — Football.** USC at Los Angeles Hilton Hotel. Wednesday-Thursday.

June 5-7—**Highlights of Ophthalmology.** PMC. Thursday-Saturday.

June 5-7—**Sacramento Valley Counties Regional Postgraduate Institute.** California Medical Association in cooperation with UCSF and Sacramento Valley Counties Medical Societies. Sahara Tahoe Hotel, Lake Tahoe. Thursday-Saturday. $20. Contact: CMA.

June 6-7—**Vectorcardiography.** UCSF at Mt. Zion Hospital. Friday-Saturday.

June 7 — **Office Management.** UCLA at St. Joseph's Hospital, Burbank. Saturday.

June 9-11—**American Neurological Association.** Beverly Hilton Hotel, Los Angeles. Monday-Wednesday. Contact: Samuel Trufant, M.D., Cincinnati General Hospital, Cincinnati 45229.

June 10-14 — **Electrophoresis Workshop.** UCSF at Children's Hospital. Tuesday-Saturday.

June 11-13—**Fractures.** USC. Wednesday-Friday.

June 14-15—**Sex Disorders in Clinical Practice.** UCSF. Saturday-Sunday. $25.

June 18—**My Third Year of Residency Training with Professor Carstairs.** Agnews State Hospital, San Jose. Wednesday. Contact: J. Elizabeth Jeffress, M.D., Director of Professional Education, Agnews State Hospital, San Jose 95114.

June 19-21—**American Medical Women's Association.** Alta Mira Hotel, Sausalito. Thursday-Saturday. Contact: Mrs. Gertrude F. Conroy, 1740 Broadway, New York 10019.

June 20-21—**Postgraduate Seminar: Pediatrics.** Children's Hospital of Orange County, Orange. Friday-Saturday. $30. Contact: Merl J. Carson, M.D., Medical Director, Children's Hospital of Orange County, 1109 West La Veta Avenue, Orange. (714) 538-8831.

June 23-25—**Postgraduate Course in Ophthalmology.** Stanford University. Monday-Wednesday. $100. Contact: Division of Ophthalmology, Stanford University School of Medicine, Stanford 94305.

June 25-27—**Tenth Annual Pediatric Seminar.** Children's Hospital, San Diego at Hanalei Hotel, San Diego. Wednesday-Friday. Contact: H. Wayne Cleeton, Assistant Administrator, Children's Hospital, 8001 Frost Street, San Diego 92123.

June 28-29—**Nasal Reconstruction.** UCLA. Saturday-Sunday.

JULY

July 2-6—**Seminars for General Practitioners.** UCLA at Lake Arrowhead. Wednesday-Sunday.

July 11-12—**Pediatric Allergy.** PMC. Friday-Saturday.

July 24-26—**Strabismus Conference.** PMC. Thursday-Saturday.

California
Medicine

Cystic Fibrosis of the Pancreas

Diagnosis by Sodium Electrode Sweat Tests

SAUL FRIEDLANDER, M.D., ROBERT E. GASBER, M.D., AND LARRY M. LIEB, M.D., *Sacramento*

■ *One of the most difficult and unreproducible procedures in clinical laboratories has been the measurement of electrolytes in sweat. The iontophoresis techniques for the diagnosis of cystic fibrosis of the pancreas, which are widely used, are fraught with difficulties.*

Measurement of sweat electrolytes with sodium or chloride electrodes is gradually replacing the iontophoresis methods. A simple modification of the sodium electrode technique was used for diagnosis in 11 cystic fibrosis patients and in 260 normal children. The values obtained with the sodium electrode clearly separated the normal children from those with cystic fibrosis.

IN RECENT YEARS, iontophoresis has been used extensively to measure sweat electrolytes to diagnose cystic fibrosis of the pancreas.[1] The iontophoresis technique has been a very difficult procedure in most laboratories, and carries a slight risk to the patient. In infants it is often impossible to obtain enough sweat by iontophoresis to give accurate electrolyte measurements. An important contribution to the diagnosis of cystic fibrosis was made by Goldbloom and Sekelj,[2] who developed an ingenious technique for determining the sodium concentration of sweat, using a special sodium electrode applied to the skin surface. Warwick[3] described a modified heated chloride electrode test, which is somewhat more complicated than the procedure we are using. The technique of Hansen and coworkers,[4] using a chloride electrode, is more complicated and time-consuming.

Since June 1964, we have used the sodium electrode in place of iontophoresis to determine sweat sodium ion concentration. We have modified the technique of Goldbloom and Sekelj, using a simpler method. This report confirms the findings of Goldbloom and Sekelj and describes the use of the sodium electrode with our modified technique in 22 normal adults, 11 children with cystic fibrosis, and 260 normal children.

Instrumentation and Methods

A Beckman combination electrode A 78420V was used to measure the concentration of sodium ion on the surface of the skin. This electrode, unlike the usual glass electrode, is filled with a mixture of KCl and AgCl. A Beckman pH meter-voltmeter was used to measure direct voltage, employing the expanded scale. The electrode when first put into use was calibrated by measuring the potentials obtained with solutions of known sodium ion concentration at various temperatures. The values were plotted on semi-log paper. Slight

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The authors are pathologists, Mercy General Hospital, Sacramento.

Submitted, revised, 17 January 1969.

Reprint requests to: Mercy General Hospital Laboratory, 4001 Jay Street, Sacramento 95819 (Dr. Friedlander).

differences in the potentials were found at different temperatures. Goldbloom and Sekelj used a thermistor to correct for variations in the skin temperatures of the patients.

To eliminate the use of a thermistor, we developed a technique in which the voltage obtained from the center of the patient's palm was compared with the voltages obtained after thin layers of at least three standard solutions of sodium ions, poured onto the palm, were allowed to equilibrate with the skin temperature. Equilibration occurred within a few seconds. This technique corrected for skin temperature and also gave a new accurate calibration curve for each case. To determine the patient's own sweat sodium concentration, the patient's hands were washed with soap, thoroughly rinsed with tap water, rinsed with distilled water, and dried with clean towels or Kimwipes® (absorbent paper). Kimwipes or properly laundered towels did not change the sweat sodium. The rubber collar was slipped above the round opening in the electrode glass before use. The electrode was then applied against the skin with an even firm pressure. For the measurement of the intrinsic sweat sodium concentration, it was necessary to wait about three minutes after drying the skin, to allow enough sweat to appear on the skin surface to give accurate, stable voltage readings. We did not find it necessary to use external heat in the manner described by Hansen and coworkers.[4] The waiting period was not necessary in measuring the potentials of the standard solutions on the skin. The tests were done in duplicate or triplicate.

Between applications of the electrode to the skin, the tip of the electrode was washed with distilled water from a squeeze bottle and gently wiped with Kimwipes. We found that the sodium concentration of the sweat of the skin in the center of the palm was different from the concentration in the skin overlying the metacarpal folds and the thenar and hypothenar eminences. The center of the palm was the most convenient area for determining voltages.

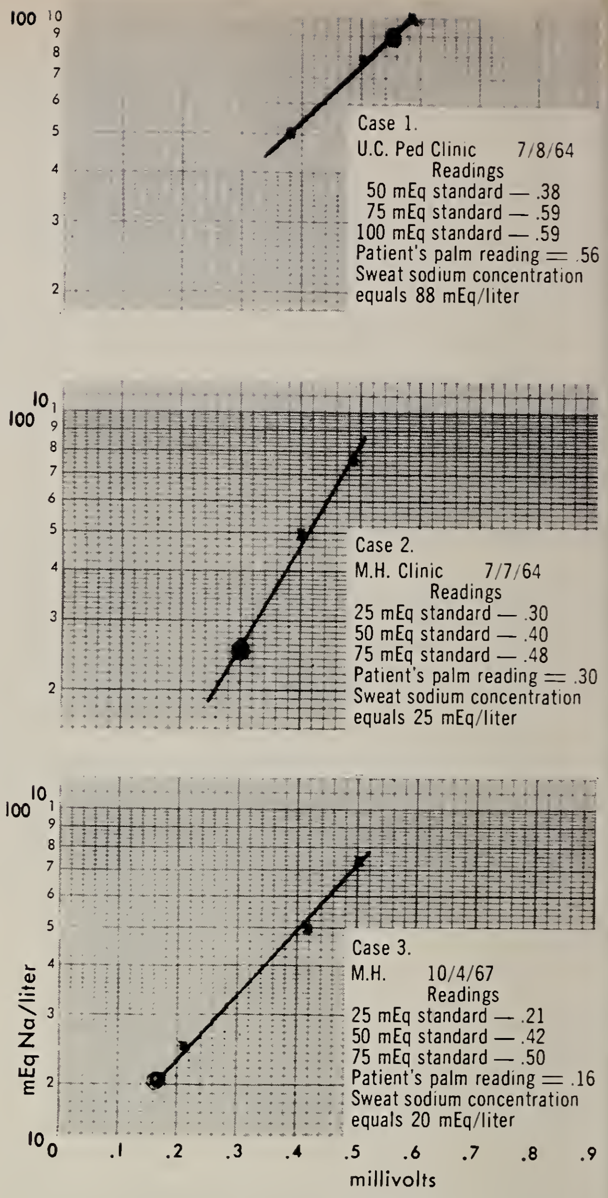

Chart 1.—Sweat sodium concentration measurements on one patient with cystic fibrosis (Case 1) and two normal children (Cases 2 and 3).

If the electrode was stored in distilled water or in a high concentration of sodium ion, its performance was erratic, with considerable instability and voltage drifting. This instability was avoided by immersing the electrode in a standard 10 mEq per liter sodium solution when not in use. Sodium standards were easily prepared from our stock solutions used for flame photometry. Working solutions of standard containing 10, 25, 50, 75, 100 and 125 mEq of sodium per liter were used. Higher concentrations were required in a few cases. The standards employed in each test were selected to give potentials bracketing the intrinsic potential found on the skin. The voltage readings of the standards were plotted on three-cycle semilogarithmic paper (Chart 1), usually used for three tests, and the voltage reading of the patient's palm was converted to mEq Na per liter from the straight line obtained with the standards (Chart 1). Unlike the usual glass electrodes used for pH

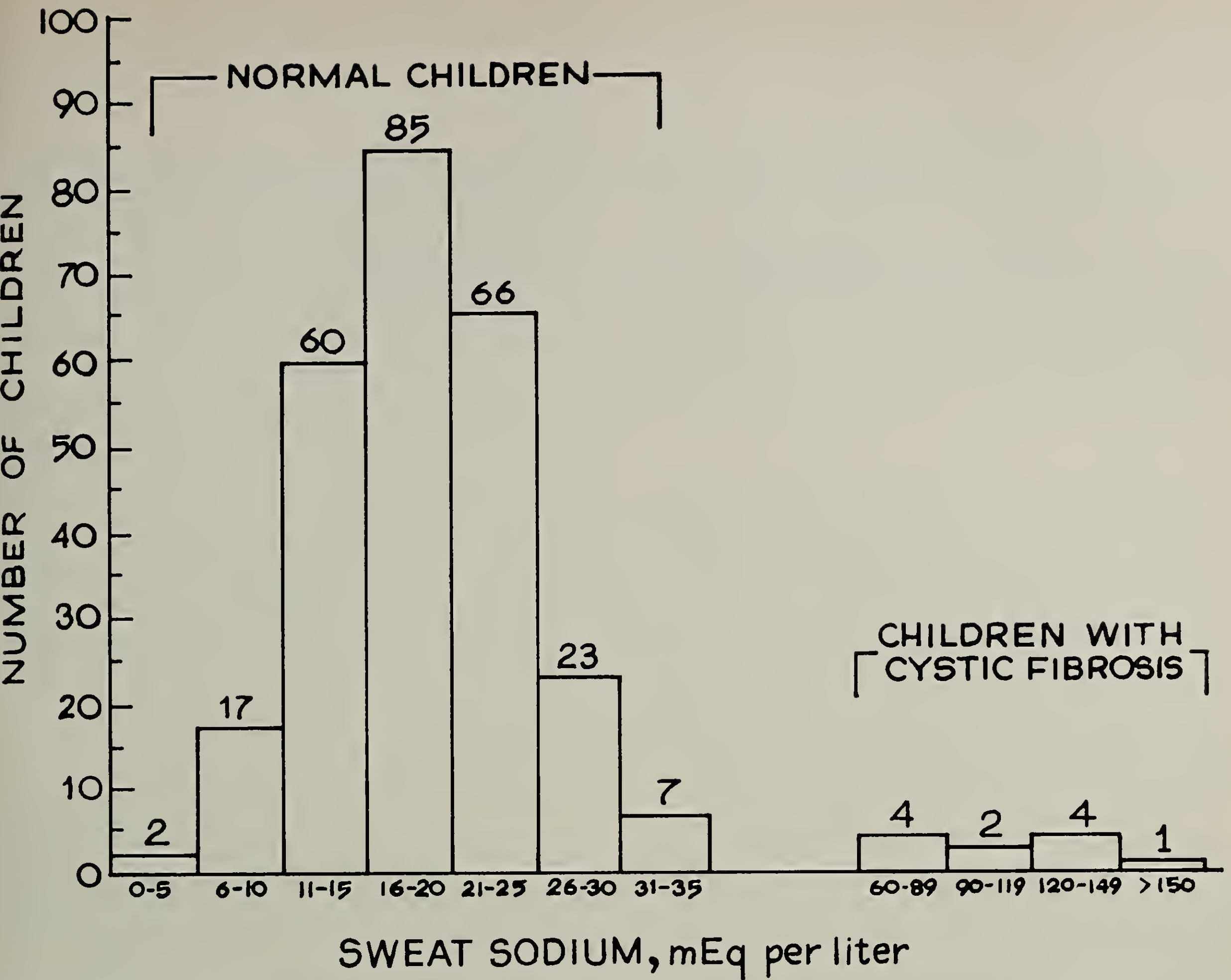

Chart 2.—Note that the highest sweat sodium value in 260 normal children was 35 mEq per liter. In the 11 cystic fibrosis patients, the sweat sodium varied from 60 to 184 mEq per liter.

determinations, the sodium electrode was not rendered unstable by static electricity. On two occasions, technicians when storing the electrode in 10 mEq NaCl left the rubber collar off the round hole in the electrode glass wall, and the NaCl solution mixed by convection with the KCl-AgCl solution within the electrode, so that readings were unobtainable. This defect was easily corrected by emptying the electrode with Pasteur pipettes, and refilling with the proper KCl-AgCl solution.

Patient Material

Electrode sweat sodium concentrations first were measured in normal adults in our laboratory. In June, 1964, through the courtesy of Dr. Louise Yeazell, Associate Professor of Pediatrics at the University of California, and with the help of Dr. Herman Lipow, who was working in the Cystic Fibrosis Clinic at that time, our instruments and solutions were taken by one of us (S.F.) on several occasions to the University of California Cystic Fibrosis Clinic, and measurements were taken on six children with known cystic fibrosis, and on ten patients who were considered normal. In our laboratory we have studied over 255 children from Mercy Childrens Hospital and Mercy Hospital Childrens Clinic, as well as patients referred from other hospitals. Five of these patients had high sweat sodium levels correlated with cystic fibrosis.

Results

Chart 1 compares the findings in two normal persons and one cystic fibrosis patient, and demonstrates our method of calculating results on semilog paper. Chart 2 is a frequency distribution curve showing the sweat sodium concentrations of 260 normal children and 11 children with known cystic fibrosis. None of the normal adults had sweat sodium concentrations higher than 50 mEq per liter. None of the normal children had sweat sodium concentrations higher than 35 mEq per liter, and the mean was 19 mEq. The lowest sweat sodium concentration in a patient with cystic fibrosis was 60 mEq per liter. The mother of two brothers with cystic fibrosis had a sweat sodium concentration of 67 mEq per liter. The father of this patient had a sweat sodium concentration of 41 mEq per liter.

Discussion

In our experience, the sodium electrode is the best instrument for the determination of sweat sodium ion concentrations. With the iontophoresis technique it is often impossible to get enough sweat from babies to give accurate results. The iontophoresis procedure took at least two hours of a technician's time, compared with 15 or 20 minutes required to obtain duplicate standardizing curves and sweat tests with the sodium electrode.

The application of standard solutions to the patient's skin corrects for the temperature variations in the skin. In all of our curves, at least three points were determined with different sodium standards on the skin, and these points almost always produced a straight line on semi-log paper. If a straight line was not produced, either one of the standards was inaccurate or the reference battery of the pH meter-voltmeter needed to be replaced. The reference battery should be replaced every four months. The electrodes lasted about 18 months.

The findings with the sodium electrode were comparable to those obtained with a chloridometric method used at the University of California. We have not presented the correlation with those chloridometric determinations, because those measurements were made one to six weeks before our tests. The values we obtained with our previous iontophoresis-flame photometer sodium and colorimetric chloride tests were not reproducible enough to be used to check the sodium electrode method, which was reproducible.

A high sweat sodium concentration test alone does not make the diagnosis of cystic fibrosis. However, in all of our patients there was a sharp differentiation between normal and abnormal findings, which correlated well with the clinical diagnosis.

REFERENCES

1. Gibson, L. E., and Cooke, R. E.: Test for concentration of electrolytes in sweat in cystic fibrosis of pancreas utilizing pilocarpine by Iontophoresis, J. Pediat., 23:545-549, 1959.

2. Goldbloom, R. B., and Sekelj, P.: Cystic fibrosis of the pancreas: Diagnosis by application of a sodium electrode to the skin, New Eng. J. Med., 269:1349-1352, 19 Dec. 1963.

3. Warwick, W. J.: Cystic fibrosis sweat test for newborns, JAMA, 198:59-62, Oct. 1966.

4. Hansen, L., Buechele, M., Koroshec, J., and Warwick, W. J.: Sweat chloride analysis by chloride ion-specific electrode method using heat stimulation, Am. J. Clin. Path., 49:834-841, June 1968.

MALABSORPTION OF FAT DUE TO CHOLESTYRAMINE

"One of a number of drugs that can significantly alter the intraluminal environment of the gut is the anion exchange resin cholestyramine (Cuemid or Questran) used for relief of itching in jaundiced patients and suggested for use in lowering serum cholesterol. This agent binds bile salts within the intestinal lumen. The amount of bile salts then available for micelle formation, which is necessary for normal fat absorption to proceed, is thus greatly reduced; and significant malabsorption of fat results whenever cholestyramine is administered in large doses."

—Jerry S. Trier, M.D., Albuquerque

Extracted from *Audio-Digest General Practice*, Vol. 16, No. 45, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

Psychological Aspects of Cystic Fibrosis in Children and Adolescents

JOSEPH D. TEICHER, M.D., *Los Angeles*

■ *Medical care of children with cystic fibrosis has been so greatly improved in recent years that many are now reaching adolescence and early adulthood. Traversing adolescence is a trying task for any chronically ill child, but even more difficult for the cystic fibrosis patient. Clinicians report that many of these adolescents have problems for which the patients, the family, and the practitioners need help. The key to dealing with the problems is to attempt to approach "normality" of living as closely as possible as early as possible despite the risks inherent.*

MANY CHILDREN WITH CYSTIC FIBROSIS now reach adolescence and at least early adulthood, and this extension of life brings with it a host of special problems. Adolescence is difficult enough without having a serious handicap like cystic fibrosis.

The Patient

Understandably, the cystic fibrosis child is the object of considerable attention not only medically but at home and at school as well. While this attention is necessary, it creates an especially difficult milieu for healthy personality development. This is a trying task for any chronically ill child; but with a genetically determined illness requiring life-time care, the taking of medicines, the use of mechanical apparatus and living in constant danger of respiratory infections, it is enormously complicated for the family, for the community and for the developing child. Parents soon learn that cystic fibrosis rivals cancer as a cause of death up to age 15. Despite all this, the goals of acceptance of illness, limitations, strengths, adequate peer adjustment, schooling, planning for the future and counsel on the problems of adulthood with its special implications for work and marriage can be attained. Fortunately, if the disease is detected early enough many patients are saved from its gravest consequences.

Cystic fibrosis can be a staggering economic drain. Costs of drugs, equipment and other items are large. What cannot be measured are the costs of round-the-clock watchfulness and attention by parents and often siblings, the demanding schedule of visits to doctors, clinics or cystic fibrosis centers, and the strain on family relationships. New problems arise when care of the patient absorbs so much of the parents' time and energy that brothers and sisters feel left out. If there is more than one child with cystic fibrosis in the family, the pressures on overworked, worried mothers and fathers are enormous. It is burdensome just to know that, regardless of the care, cystic fibrosis cannot be outgrown. However, there is some relief in the knowledge that with proper medical and psychological care reasonably average lives can be led by most patients. Small children don't know all the facts of their prospects, but adolescents usually do.

Thirty percent of the known cystic fibrosis pa-

Submitted 26 November 1968.

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tients in the United States are now older than 12 years. Clinicians[1] report that the adolescents present problems of immature behavior and unusual dependence on parents and that they openly blame parents for anything that goes wrong with the progress of treatment. Sometimes there is complete renunciation of all therapy routines by patients who declare they wish to die soon; and it is reported that in one case a patient did die early for this reason. Episodes of suicide attempts by overdose of medication or sedative are reported. Other patients are averse to attending school because of the embarrassing frequency of bowel movements. Experience with many adolescents who accept jobs has been generally poor; they seem unable to follow through on many tasks that demand self-discipline.

Even healthy youngsters have difficulty in adjusting to adolescence. Consider, then, the special handicap of cystic fibrosis. The most serious effects result from the abnormal mucus produced in various organs. It becomes a thick, gluey substance that clogs the bronchial tubes, and by plugging the pancreatic ducts interferes with the digestive enzymes. Respiratory infections are an ever-present danger, making school a hazard. The patient may taste salty when kissed. He does a great deal of coughing at home and in school; and it is embarrassing, but cough he should. Special aerosol treatments, inhalation of antibiotics, and sleeping in a plastic tent into which a mist of water and propylene glycol is pumped by a compressor are common. His room looks like a power plant. The child does not have the stamina to play with others on equal terms and often this is a cause of embarrassment.

Physically he is often thin, smallish with a slightly protruding abdomen, with somewhat discolored teeth and a mild clubbing of the fingertips. Yet he is a big eater, often asking for seconds or even third helpings. Usually he will avoid starches in large amounts, also fatty and greasy foods like potato chips and peanuts. He has to take pills, he has to be excused more often than usual from school classes because of increased bowel movements, and he sweats excessively (often needing extra salt in his food for that reason).[2]

Most children, even with the awesome paraphernalia often required in cystic fibrosis, make their own adjustments in a way which is difficult for the normal person to comprehend. Parents who insist on the child's doing as much for himself as is reasonable and that he have his duties and responsibilities within the limits of his disability have the correct approach. Discipline is necessary; otherwise he will not develop "inner brakes" so essential in adolescence and later life. His life should be made as interesting as possible with books, games and new experiences. He must be made to recognize that the illness and the elaborate methods of care are nothing to be ashamed of. He must know that the disease cannot be cured and must be borne as others bear other difficulties. Obviously, the school must help the child accept himself and shelter him from teasing and cruel behavior from his peers should it occur. The child should understand what the limitations are on his activities and the reasons for them. When difficulties arise at school or in the home, parents should not automatically take his part because he is ill.

The Parents' Role

Parents who have a handicapped child and especially one with a grim prognosis are understandably concerned and anxious. Many also have feelings of guilt and may be accusing of the spouse —guilt because they feel they have been punished in the form of the ill child and accusing of the spouse as if it were her (his) side of the family tree responsible. Some parents consciously or unconsciously wish for the suffering child to die, and this may be reflected in their care or denial of care for the child. Where so much care is involved, it is difficult and yet essential that overattention, overindulgence and oversolicitude be avoided, for that would truly deprive the chronically ill child of age appropriate experiences and stunt his emotional development. It is too easy to subordinate all to the care of the sick child, to have the entire household focus around his care. The more anxious and guilt-ridden the parent, the easier it is to slip into this attitude.

A handicapped child cannot be expected to have the satisfaction of being just like other children—a difference which must be faced by him and his parents realistically. Parents often identify too closely with the child and read into him the reactions they believe they would have in similar circumstances. Any show of pity should be avoided. Self pity becomes an excuse for failure, a means to enlist sympathy and to tyrannize parents and siblings. Personalities are warped because of poor understanding of illness and unhealthy attitudes of parents.

Physicians have a crucial role to play in supporting the parents, in helping outline the regime other than medical and in being so much aware of the child's emotional development as they are of his medical condition. More, physicians must help parents to lead reasonably normal lives, with interests outside the home. Parent groups sharing their experiences is of much help. While an unusual amount of time is necessarily spent caring for a child with cystic fibrosis, and often the threat of death is prominent, the other children in the family must not be neglected. They have their right to develop normally and to be sustained by parental nourishment and support.

Spending time in a hospital is a common experience for a child who has cystic fibrosis. Some children die and the fear of death hangs chronically over parents and child. Children between the ages of three and five years simply have no comprehension of the idea of death; they cannot conceive of lifelessness. From five to nine years, children recognize death, but without exception regard it as a person. From the ninth year children achieve a realistic conception of death as a permanent biologic process, and the fear of it is urgent, pervasive and persistent in the chronically ill older child and adolescent.[3]

The Mother-Child Relationship

For a child in a hospital, his mother's absence is a notable cause of distress. While some adapt well and relate to the nursing staff, others seem never to tolerate maternal absence and are quite irritable and withdrawn. This has little relationship to the clinical condition of the child. The various mechanical procedures and the often necessary venipunctures are distressing to him. The death of another child in the hospital affects parents and staff too. In the older age group many children become anxious, depressed and withdrawn. In younger children anxiety about death is present in more subtle forms, although overshadowed by fear of separation or fear of the various procedures.

The threat of death to the child poses a symbolic threat of death to the mother; the mother-child relationship is the most reciprocally intense of interpersonal relationships. Some studies[4] of mothers of fatally ill children (not with cystic fibrosis) showed most reacting in a disbelieving manner, tending to deny either the diagnosis of the disease or its possible fatal outcome. They wanted to be with their children as much as possible, often without much regard for the needs of the remainder of the family. They wanted, sometimes in an irrational manner, to try anything in the way of new treatment that might offer hope for cure. Interestingly, in Natterson's series of fatally ill children who were ill for a long time, the most common reaction of the mothers was calm acceptance of the foreknowledge of fatal outcome. There was almost no tendency to weep; in some instances the mother expressed a wish that the child die so his suffering would be ended. There was no expression of guilt. When the children of such mothers actually died, there was a mixed expression of calm sorrow and relief. Other reactions included hysteria. The longer the parents knew about the fatal illness, the more integrated the terminal reaction.

The traumatic announcement to the mother of the diagnosis and prognosis in effect constitutes an immediate rupture of the normal mother-child relationship. The mother identifies with the child very strongly; the pain therefore is intolerable, and attempts to deny the reality of the illness are blatant and common. Where the illness is serious and a fatal outcome possible or probable, a mother can work out a psychic separation from the child. The mourning process has begun. Finally, often with acceptance of death as the outcome, a mother may openly and guiltlessly express wishes of death for the child.

In Adolescence

It is a long way to adolescence but so is the perilous course of cystic fibrosis. Healthy or sick, an adolescent wants to belong to his peer group, to be active and independent, to feel attractive and not different. He is conscious of bodily sensations, he has sexual drives and aims that he wishes to satisfy, and he wants to look to a future and to be a somebody. Yet the adolescent with cystic fibrosis, even in the healthiest possible parental and family environment, has a difficult task. How can he establish autonomy—so important to an adolescent—when all too often he needs help with mechanical aids? How is one going to be attractive to the opposite sex when it is disconcerting to cough, have to go to the toilet often, be unable to keep up with one's peers athletically, be so excessively and necessarily careful about catching colds, and even taste salty? The full impact of cystic fibrosis is well known to the adolescent. He knows he is the result of defective genes and that he carries them. All too often he is bitter toward his parents for having him and for "cursing" him with such an illness. Frequently he is depressed with feelings of hopelessness for the future. The adolescent with cystic fibrosis knows that if he does not take care he will die as a consequence. Every stereotype of the red blooded young American is violated in cystic fibrosis; every task of adolescence is seemingly insurmountable.

The adolescent struggles with dependency which is enforced by the illness. The greater the dependence the greater the maturational struggle for independence even to the point of dissocial behavior. The key is that in the case of an adolescent where much care appears necessary or is demanded, the parents have enforced a dependent attitude, have not permitted independent activity and self responsibility when it was possible. Given this, parents do not give up their hovering anxiety, however understandable, and continue to cripple the adolescent in any effective functioning or responsibility, like holding a job.

Patients who attempt suicide, exhibit dissocial behavior or who avoid taking care of themselves —a form of suicide—are depressed, angry, feel hopeless, helpless and isolated by virtue of their illness. Important, too, is the depression of the parents who are concerned with their youth's future. Some parents give the message, "I wish you were dead." Many young people oblige. The youths share their parents' hopeless attitude for the future, and share their parents' feelings of guilt, shame, hostility.

Even so, it is not impossible for an ill child or adolescent with cystic fibrosis to be effective, to achieve a sense of identity that is not necessarily one of helplessness and child-like dependence. The task must begin at the beginning—in work with parents and children just as soon as the cystic fibrosis is recognized. It is not enough to do what is medically necessary; one must actively intervene with the family and ameliorate the psychological stresses as soon as possible. This implies the physician and allied medical personnel not only must be much better informed psychologically but, more, must make the time to apply their knowledge throughout the developmental span. This may be done in individual help, in family therapy and in group therapy. Whatever appears to work is worth trying. To keep one medically alive for a psychological death is not a medical success.

Additional Comments

At the Yale Child Study Center nursery school, children with cystic fibrosis were encouraged to attend. Respiratory infections are frequent in nursery schools. The risk was explained to parents and the calculated risk is the step toward as much normality as is possible to achieve. Dr. Senn and his staff practice preventive guidance with all their families in sickness and health. From the earliest days on, "normality" is practiced as much as possible.[5]

Adolescence with its fluidity presents a fine opportunity to resolve what has not been accomplished earlier. The task is enormously difficult with patients who have cystic fibrosis, and to date generally unrewarding to psychiatrists, who have shown little interest. This will change, and while success will not be great at first, at least a start will have been made. The grimness of the illness, the spectacular medical success as measured by increasing longevity, and the fact that the disease is genetically determined and incurable are harsh realtities for even the healthiest parents to absorb. In dealing with patients who have cystic fibrosis it behooves medical practitioners to practice total medicine—psychological and biologic—from the earliest days of infancy. In cystic fibrosis with all its limitations, all reasonable calculated risks to help toward normal living are worth taking. This requires much work with the family. Also, allied health care specialists are becoming increasingly involved and will be more and more helpful in assisting with the development of the chronically ill child as well as supporting the family to achieve as much normality as is possible.

Finally, marriage is a huge step for persons with cystic fibrosis—and for their mates. But it is possible and desirable. In view of the genetic damage, however, every effort should be made to prevent the couple's having their own children. They can experience the pleasures of parenthood and raising healthy children by adoption or foster care.

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Cancer of the Nasopharynx

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■ *Of 75 consecutive patients with nasopharyngeal cancer treated at UCLA Center for Health Sciences, 42 were eligible for long-term study. Fourteen (33 percent) survived five years, and one survived ten years. Since the management of nasopharyngeal cancer is primarily irradiation, a well-planned aggressive treatment program using supravoltage therapy is recommended. In spite of cranial nerve involvement or skull erosion, radiation therapy occasionally may offer long term control of the disease.*

THE DIAGNOSIS OR recognition of malignant lesions involving the head and neck while they are still in a localized stage is most important. A high proportion of localized head and neck cancers can be cured by surgical operation or radiation therapy or a combination of these two means. It is surprising that many patients are still seen with extensive malignant disease of the head and neck region. This may be owing in part to want of thorough examinations of the head and neck regions or of prompt biopsy of suspicious lesions, and sometimes to a patient's neglecting to consult a physician. Painful lesions have frequently been treated with antibiotics with an improvement of symptoms resulting in delay of biopsy and then a period of delay before the beginning of definitive treatment.

After the diagnosis is made and the extent of the disease determined, the first physician who makes the decision as to the method of therapy bears responsibility for the final outcome. If the therapy selected is inadequate or not appropriate, subsequent therapy will be much less effective.

The primary lesions may initially produce few if any symptoms and the first indication of disease may be the presence of metastatic disease in the nodes of the neck. For example, a high proportion of patients with primary cancer of the nasopharynx have metastatic disease in the neck when first examined. Primary nasopharyngeal cancers make up 1 to 2 percent of all cancers.

Patients with an enlarged lymph node in the neck suspected of containing metastatic disease should have a thorough examination (repeated several times if necessary) of the head and neck regions before the lymph node is removed for biopsy. The removal of a cervical lymph node before thorough examination of the head and neck region has been done may delay the treatment of the primary cancer and interfere with subsequent surgical operation if it is indicated.

Although the nasopharynx is accessible to examination, it is often referred to as an anatomic "blind spot." It is mandatory to recognize the symptoms produced by lesions in this area so that the prompt diagnosis and treatment necessary to improved results can be achieved.

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Presented before the Section on Radiology at the 97th Annual Meeting of the California Medical Association, San Francisco, March 23 to 27, 1968.

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Sex and Age Incidence

Between October 1955 and January 1968 there were 75 patients with cancer of the nasopharynx admitted to the UCLA Center for Health Sciences. Histological verification was obtained in all cases but one.

The average age of the patients was 45.5 years; the range from 6 to 90 years. The ratio of males to females was 3:1. Three of the 75 patients were Chinese and one Japanese.

Histological Classification

The most common types of nasopharyngeal malignant lesion in this series were epidermoid carcinomas (38, or 50.6 percent), followed by unclassified carcinomas (12, or 31.6 percent), transitional carcinoma (eight, or 10.6 percent), lympho-epithelioma and adenocarcinoma (five of each, 6.6 percent), lymphosarcoma and plasmocytoma (two each, 2.6 percent) and 3 or 4 percent miscellaneous types of sarcoma. (See Table 1.)

Presenting Symptoms

The outstanding finding when the patients were first seen was cervical lymphadenopathy, which was noted in 42 (56 percent) of the patients. Other significant findings were earache, tinnitus, otitis media or loss of hearing in 25 (33.3 percent) headache in 22 (29.3 percent), cranial nerve signs in 20 (26.6 percent) and nasal obstruction, epistaxis or bloody nasal discharge in 19 (25.3 percent). Roentgenographic evidence of skull erosion was seen in 12 (16 percent) of the patients (Table 2).

TABLE 2.—*Presenting Symptoms When First Seen Nasopharyngeal Cancer (75 cases)*

	No. of Pts.	*%*
Cervical lymphadenopathy	42	56.0
Earache, tinnitus, otitis media, loss of hearing	25	33.3
Headache	22	29.3
Cranial nerve signs: diplopia, facial pain, facial palsy, hoarseness, dysphagia	20	26.6
Nasal obstruction, epistaxis, bloody discharge	19	25.3
Sore throat	4	5.3
Roentgenographic evidence of skull erosion	12	16.0

Stage of Disease and Results

The method of staging advocated by Geist-Portman[1] was used. This method of staging is as follows:

Stage I. Cancer limited to the nasopharynx.

Stage II. Nasopharyngeal cancer and palpable cervical lymph nodes.

Stage III. Nasopharyngeal cancer with involvement of cranial nerves and or skull erosion.

It is interesting to note that eight of eighteen patients (44.4 percent) who had Stage II carcinomas were alive five or more years, and that two of seventeen patients (11.6 percent) who had Stage III lesions survived for five or more years free of disease. The overall five-year survival rate for patients was 33.3 percent. These results compare most favorably with other reported results. Eight of 27 patients (29.6 percent) who had primary nasopharyngeal cancer and had involvement of the nodes in one side of the neck survived for five years or more (Tables 3, 4 and 5).

It is recommended that radical neck dissections not be done until a full course of radiation therapy

TABLE 1.—*Histological Classification of Nasopharyngeal Tumors*

Classification	*UCLA*	*UC-SF*	*Memorial Hospital, New York*[2]	*M. D. Anderson Hospital, Houston*[3]	*Presbyterian and Montefiore Hospitals, New York*[4]
Epidermoid carcinoma	38 (50.6%)	14 (17.1%)	17 (19.5%)	53 (47.3%)	27 (43.0%)
Transitional carcinoma	8 (10.6%)	33 (40.3%)	42 (48.3%)	..	..
Lympho-epithelioma	5 (6.6%)	25 (30.5%)	14 (16.1%)	42 (37.5%)	20 (31.7%)
Lymphosarcoma	2 (2.6%)	4 (4.9%)	11 (12.6%)	10 (8.9%)	12 (19.1%)
Adenocarcinoma	5 (6.6%)	2 (2.4%)	3 (3.5%)	1 (0.9%)	3 (4.8%)
Plasmocytoma	2 (2.6%)	..	..	1 (0.9%)	1 (1.4%)
Unclassified	12 (31.6%)	..	..	4 (3.6%)	..
Miscellaneous sarcoma	..	3 (4.0%)	3 (3.6%)	..	..
Embryonal sarcoma	..	1	..	..	..
Neurofibrosarcoma	1	1	..	..	..
Myxofibrosarcoma	..	1	..	..	..
Chondrosarcoma	1	..	..	..	..
Rhabdomyosarcoma	1	..	..	..	..
Fibrosarcoma	..	..	..	1 (0.9%)	..
Total	75	82	87	112	63

TABLE 3.—*Comparison of Five-Year Survival Rate and Staging (Geist-Portman[1]) in Four Reported Series*

Author	*Stage of Disease* *I* *Limited to nasopharynx*	*II* *Nasopharynx and palpable cervical nodes*	*III* *Nasopharynx cranial nerves and/or skull erosion*	*Overall 5-year survival rate*
Geist-Portman[1]—1951	3/13 (23.0%)	1/17 (6.0%)	0/ 8	4/ 38 (10.0%)
Vaeth[5]—1959	11/16 (68.8%)	11/40 (27.5%)	1/26 (3.9%)	23/ 82 (28.2%)
Yeh[6]—1961	7/ 9 (77.7%)	13/59 (22.0%)	8/51 (15.6%)	28/119 (23.5%)
UCLA—1968	*4/ 7 (57.1%)	*8/18 (44.4%)	2/17 (11.6%)	14/ 42 (33.3%)

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*Two patients died of intercurrent diseases (CVA and cirrhosis of liver).

has been given, extending from the base of the brain to the clavicle on each side with a tumor dose of approximately 6,000 rads in about six weeks, and the results of this therapy have been determined. The vocal cords are shielded during the radiation therapy. Megavoltage radiation therapy is preferred because of the relative uniformity of absorption of the ionizing radiation in muscle, fat and bone. The cervical lymph nodes are treated in all cases, even though the lymph nodes may not be enlarged to palpation.

TABLE 4. — *Five-Year Survival Rates Associated with Cancer of the Nasopharynx at Various Treatment Centers*

Series	*No. of patients*	*5-year survivals (%)*
University of California Medical Center, Los Angeles............	42	14 (33.3%)
University of California Hospital, San Francisco[5]	82	23 (28.2%)
New York Hospital, Cornell Medical Center, New York[7].............	44	13 (29.5%)
Massachusetts General Hospital, Boston, Mass.[8]	104	36 (34.5%)
Los Angeles Tumor Institute, Los Angeles[9]	24	8 (33.0%)
Memorial Hospital, New York[2].....	87	20 (23.0%)
Middlesex Hospital, London, England[12]	54	8 (15.0%)
Presbyterian and Montefiore Hospitals, New York[4]	44	13 (29.6%)
Radium Center, Copenhagen, Denmark[10]	77	11 (14.3%)
Lahey Clinic, Boston, Mass.[11]......	39	13 (33.3%)
Institute of Pathology, National Taiwan University, Taipei, Taiwan[6]	119	28 (23.5%)
M. D. Anderson Hospital, Houston, Texas[3]	85	32 (38.0%)

TABLE 5.—*Incidence of Cervical Lymphadenopathy and Five-Year Survival Rate in 42 Patients with Nasopharyngeal Cancer*

	No. of Pts.	*5-Year Survivals*
Ipsolateral Nodes (positive).......	27	8 (29.6%)
Ipsolateral Nodes (negative).......	9	5 (55.5%)
Bilateral Nodes (positive)........	6	1 (16.6%)
Total (5 Year)..............	42	14 (33.3%)

The significance of cervical lymphadenopathy can be illustrated by the fact that 55 percent of patients with negative nodes and 27.2 percent of patients with positive nodes survived five years without demonstrable disease. When there are bilateral positive cervical nodes, the survival rate drops sharply (16.6 percent). Twelve patients had recurrence of cervical lymph nodes after initial irradiation. Eight of them were treated by additional irradiation (average 4,000 to 5,000 rads) to the cervical lymph nodes, and four had radical neck dissection because the primary lesions were under control. Two patients in the irradiation groups had long-term survival, one five and the other seven years. There was no long-term survival of any of the four patients in whom neck dissection was followed by further irradiation. Recurrence at the suture line occurred in all four cases.

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The Significance of Pronounc
Of Right Bun

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■ *The histories of 117 patients with left axis deviation and complete right bundle branch block* (RBBB) *on the electrocardiogram were reviewed for evidence of clinical cardiac disease, hypertension or emphysema. One hundred fifty-four patients with complete right bundle branch block alone served as controls. The incidence of coronary artery disease (myocardial infarction or angina) was significantly greater in the group with pronounced left axis deviation; the other factors evaluated showed no significant difference between the two groups. Pronounced left axis deviation of the mean* QRS *axis is associated with a high prevalence of clinical coronary artery disease. The presence of complete right bundle branch block does not alter their relationship. Some patients with complete* RBBB, *or with* RBBB *and pronounced left axis deviation, have no clinical evidence of heart disease.*

t Axis Deviation in the Presence
nch Block

THERE IS GOOD EVIDENCE that pronounced left axis deviation (LAD) of the mean QRS vector is an abnormal electrocardiographic finding, and is usually associated with heart disease.[1,2] It is an unusual finding in normal adults.[3] It is thought to be secondary to left ventricular fibrosis or anterior lateral infarction usually resulting from coronary artery disease,[4-7] with interruption of peripheral conduction fibers.[8] Complete right bundle branch block (RBBB) is not uncommon in the older age groups in which there is a high incidence of cardiovascular disease. It may be present without evidence of clinical heart disease or hypertension, even in older patients; it is not necessarily a serious lesion.[9]

In complete RBBB only the terminal portion of ventricular excitation is decidedly affected. Therefore, the initial .06-.08 seconds of the QRS complex, and the left ventricular sequence of excitation, are not greatly altered by that lesion.[10] With interruption of peripheral fibers of the superior segment of the bundle of His, as is postulated to underlie marked LAD, the sequence of left ventricular excitation is altered but not significantly prolonged, giving a QRS duration that is normal.[1] In view of these considerations, it seemed reasonable to postulate that pronounced LAD reflects the same abnormality, with or without associated RBBB. It was thought, therefore, to be of interest to determine if marked LAD in the presence of RBBB still indicates left ventricular disease, and more specifically, coronary artery disease.

Methods

Electrocardiograms of patients from the University of California Hospital, San Francisco, and the Palo Alto Medical Clinic with the diagnosis of complete RBBB were analyzed for the presence or absence of pronounced LAD. A group of 117 which met our criteria for LAD were collected, 67 from UC, 50 from PAMC. One hundred and fifty-four patients with RBBB alone served as controls, 70 from UC, 84 from PAMC. Right bundle branch block was defined as a QRS duration of 0.12 seconds or greater, RR′ or RSR pattern in V_1, and a broad slurred S in I and V_6. Pronounced left axis deviation was defined as a mean QRS frontal plane vector between —30° and —90° as determined from the electrocardiogram. The following criteria were used in determining pronounced left axis deviation: (1) $S>R$ in mm, or by area in the initial .08 second in lead II. (2) $R>S$ in mm or by area in the initial .08 second in I (to eliminate pronounced right axis deviation). Hence, this definition required a predominantly positive deflection in lead I, and a predominantly negative deflection in II and III. Instances in which the R was of greater magnitude in mm than the S in lead II, but the area of the entire S wave was larger because of

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Supported in part by USPHS grant HE 09375.

Submitted, revised, 6 January 1969.

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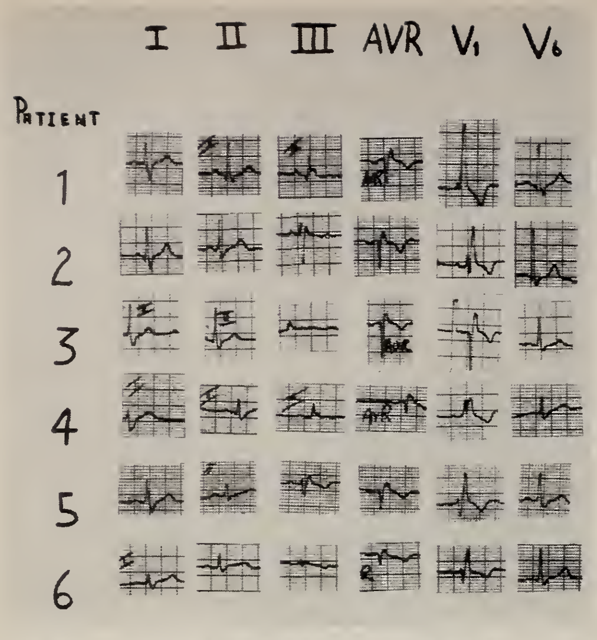

Figure 1. — Representative electrocardiograms from patients with complete right bundle branch block.

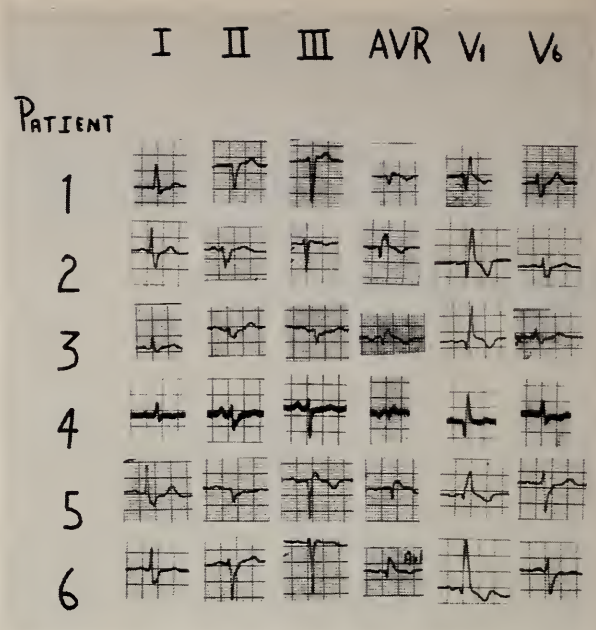

Figure 2. — Representative electrocardiograms from patients with complete right bundle branch block and pronounced left axis deviation of the mean QRS vector.

the slurring, were therefore considered to be RBBB without LAD. (See Figures 1, 2.)

The charts of these patients were analyzed for the presence of the following:

1. Angina = clinical diagnosis.
2. Myocardial infarction = if definite or very likely on the basis of considered review of the historical, electrocardiographic, laboratory, or postmortem findings available. Included was myocardial fibrosis on autopsy.
3. Congestive heart failure = clinical history, physician diagnosis, or patient receiving digitalis without a history of rhythm abnormality.
4. Hypertension = pressure greater than 150/95 mm of mercury, either or both. If labile, elevated on two or more readings in chart.
5. Valvular heart disease = systolic murmurs grade 3 or 4/4, or diastolic murmur.
6. Congenital heart disease = clinical diagnosis, catheterization findings.
7. Emphysema = clinical diagnosis, excluding “mild,” or at autopsy.
8. LVH = on physical examination, clinical diagnosis, or electrocardiogram.[11]
9. RVH = physical examination or electrocardiogram.[11]
10. Diabetes = clinical syndrome, or elevated blood glucose levels.
11. X-ray film = cardiac enlargement, excluding “possible” or “mild.”
12. Coronary artery disease (CAD) = patient with angina or infarction or both.

The chart review was conducted without knowledge of the presence or absence of LAD. Wherever indicated, an attempt was made to obtain further information from the patient’s local or previous physician, from other hospitals or from the coroner’s office.

To make the populations more comparable, all patients less than 48 years of age, the youngest of the LAD group, were eliminated, as were patients whose bundle branch block developed after surgical operation on the heart.

The presence or absence of each of the conditions evaluated (for example, angina, hypertension) in each patient was tabulated for each of the four groups: RBBB-UC, RBBB-PAMC, RBBB + LAD-UC, RBBB + LAD-PAMC. Because two somewhat different populations were represented, the groups were not combined for statistical purposes. Two-by-two contingency tables (comparing RBBB against LAD-UC and RBBB against LAD-PAMC, for both males and females) for each condition were tested by using a chi square test or a Fisher’s exact test. The significance level probabilities were combined to give one probability by using normal deviates. The data thus evaluated defined whether or not there was a significant difference in the occurrence rate of each condition in the RBBB against the RBBB + LAD groups. Those patients whose charts revealed no evidence of heart disease, or only mild hypertension, that is, 160/<95

TABLE 1.—*Age and sex of patients with Right Bundle Branch Block* (RBBB) *or* RBBB + *Left Axis Deviation* (LAD) *evaluated in this study*

	RBBB		RBBB + LAD	
	UC	*PAMC*	*UC*	*PAMC*
Number				
Male	37	60	42	35
Female	33	24	25	15
Total	70	84	67	50
Age				
Mean	68	69	70	72
Range	50-86	48-88	48-93	48-87

UC = University of California Hospital, San Francisco.
PAMC = Palo Alto Medical Clinic.

mm of mercury, or emphysema were also tabulated in both groups.

Results

There were 154 patients with RBBB, and 117 with RBBB + LAD; their ages were comparable. (See Table 1.) The frequency of the occurrence of the various conditions evaluated is tabulated in Table 2. As would be anticipated in older age groups, the incidence of coronary artery disease, hypertension, congestive heart failure, emphysema, LVH, and cardiomegaly on x-ray films was moderately high. The only conditions in which there was a significant difference (P = <.01) between the two groups RBBB and RBBB + LAD were coronary artery disease, and myocardial infarction. If overall incidence is considered, these occurred over two and three times as frequently respectively in the + LAD group. The overall incidence of angina was nearly twice as high in the LAD group, but the combined probabilities did not show a significant difference.

If one considers those patients without clinical heart disease, or only mild hypertension or emphysema or both, there were fewer such patients in the + LAD group than in the RBBB alone group (Table 3).

Discussion

It has been postulated that because of focal fibrosis or actual infarction and scarring of the myocardium which occur secondary to coronary

TABLE 2.—*Comparison of incidence of conditions evaluated in patients with* RBBB *or* RBBB+LAD

Condition Evaluated	RBBB *vs.* LAD‡	*UC*			*PAMC*			*UC + PAMC*			*Not Tab**	%†
		Female	*Male*	*Total*	*Female*	*Male*	*Total*	*Female*	*Male*	*Total*		
Angina	RBBB	7	4	11	1	15	16	8	19	27	0	18
	LAD	11	11	22	4	9	13	15	20	35	0	30
Infarction	RBBB	1	8	9	1	9	10	2	17	19	0	12
	LAD	6	16	22	4	15	19	10	31	41	0	35
Coronary Artery Disease	RBBB	8	11	19	2	17	19	10	28	38	0	25
	LAD	12	19	31	8	20	28	20	39	59	0	50
Congestive Heart Failure	RBBB	10	14	24	5	11	16	15	25	40	4	27
	LAD	9	16	25	4	14	18	13	30	43	0	37
Hypertension	RBBB	22	11	33	11	24	35	33	35	68	1	44
	LAD	16	18	34	10	15	25	26	33	59	1	51
Valvular Heart Disease	RBBB	5	2	7	2	3	5	7	5	12	10	8
	LAD	..	..	..	1	1	2	..	..	..	0	4
Congenital Heart Disease	RBBB	1	1	2	0	0	0	1	1	2	1	1
	LAD	1	1	2	0	0	0	1	1	2	0	2
Emphysema	RBBB	6	19	25	2	14	16	8	33	41	1	27
	LAD	3	17	20	1	7	8	4	24	28	1	24
LVH	RBBB	9	8	17	3	5	8	12	13	25	6	17
	LAD	9	12	21	2	2	4	11	14	25	0	21
RVH	RBBB	3	2	5	0	0	0	3	2	5	8	3
	LAD	0	4	4	0	0	0	0	4	4	1	3
Diabetes	RBBB	..	..	..	0	8	8	..	..	..	5	10
	LAD	..	..	..	1	5	6	..	..	..	0	12
X-Ray	RBBB	8	9	17	4	6	10	12	15	27	13	19
	LAD	8	15	23	4	4	8	12	19	31	8	28

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*Not Tabulated
†Total RBBB 154
LAD 117
‡LAD = RBBB + LAD

TABLE 3.—*Patients without clinical heart disease, or only mild hypertension and/or emphysema*

	RBBB		RBBB + LAD	
	UC	*PAMC*	*UC*	*PAMC*
1. No findings	8	25	8	4
2. Mild HBP	3	0	0	0
3. Mild to Mod. Emphysema	9	4	5	0
Total	20 (29%)	29 (33%)	13 (19%)	4 (8%)

artery disease, affecting primarily the left ventricle, the special conduction tissue pathways may be altered. When the superior (anterior) division of the left bundle is affected, it causes an alteration in the sequence of depolarization, the superior-anterior portion of the left ventricle being depolarized last, and gives rise to pronounced left axis deviation of the mean QRS vector. As peripheral fibers are involved, this usually occurs without a delay in depolarization as a whole, and hence no prolongation of the QRS complex.[1] Pronounced LAD has been noted in other conditions, less common than coronary artery disease, which affect the ventricular myocardium—for example, idiopathic myocardial hypertrophy,[13] obscure myocardial hypertrophy,[12] scleroderma.[14] The underlying common denominator is apparently left ventricular myocardial disease, mainly fibrosis. Although there is some alteration of the entire QRS deflection in complete RBBB,[10,15] only the terminal portion of depolarization is decidedly affected,[10] leading to widening of the QRS complex. Experimental evidence suggests that a lesion in the main right bundle is necessary to produce this abnormality; interruption of peripheral right bundle branches does not lead to QRS widening.[16]

In the light of these considerations, it is reasonable to expect that when complete RBBB and pronounced LAD occur together, each continues to reflect the same pathologic process as it does when occurring alone.

The findings of this study support this conclusion. It was anticipated that in an older age group such as was evaluated here, heart disease, hypertension and emphysema would be common. Of the conditions evaluated, only coronary artery disease occurred significantly more often, occurring twice as frequently in the RBBB + LAD group. The frequency of occurrence of the other conditions, although high, was not significantly different in the two groups. Therefore, these data substantiate that pronounced LAD is associated with a significantly higher incidence of important coronary artery disease (as manifested by myocardial infarction or angina or both) than is found in patients whose electrocardiogram does not show this abnormality, and that in the presence of complete RBBB, this association still pertains. The data also suggests a causal relationship between coronary artery disease and pronounced LAD in these cases.

It should be noted, in addition, that there are a certain number of patients who have either complete RBBB alone, or in association with marked LAD, in whom there is essentially no clinical evidence for heart disease (Table 3).

This study does not attempt to determine the precise sequence of development of complete RBBB with or without pronounced LAD in relation to the development of angina, infarction, congestive heart failure, etc.

ACKNOWLEDGEMENT

The author is grateful to Mr. Frantz Ashley, Department of Preventive Medicine, Stanford University, for his assistance with the statistics.

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Comments on the Physician's Role In Drug Abuse Work

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■ *The use of illegal intoxicating drugs by young people has reached epidemic proportions. The seriousness of the social problems underlying drug usage and the gravity of consequences for individuals and for society as a whole are a challenge to the adult world. Members of the medical profession are in a particularly strategic position to help meet that challenge. Through research, through legislative study, through clinical contacts, and through self-education and participation in community education programs, physicians can help to fulfill the responsibility of their generation for responding with integrity and intelligent leadership to this as well as to other problems of the times.*

IN THE PAST TWO YEARS there has been much attention paid a new kind of illness that is spreading rapidly and unchecked through the quiet streets of affluent suburban America. The most official name for it is "drug abuse." Attacking the young, destroying minds and souls rather than bodies, it is more insidious than the usual epidemic but in the long run it may prove more destructive and more tragic than any of the infectious diseases. In his traditional roles of community leader and protector, the physician finds himself consulted more and more frequently for help with patients who have fallen victim to the use of drugs and for assistance in planning and implementing programs designed to halt the spread of drug usage. Yet often he is not certain himself in what direction to turn, and his counsel wavers as he struggles in his own mind for answers to the doubts and questions that have become prevalent with regard to drugs. Is marijuana really harmful? Isn't tobacco infinitely worse? Dare he speak at all when his own generation has so misused alcohol and when his profession has participated in the development of a nationwide dependence on tranquilizers and sedatives? In a country torn by war and wracked by racial prejudice, can he say that the youth are not somehow justified in their philosophy of tuning in, turning on, and dropping out?

Gathering Momentum of Change

Ten years ago, in the aftermath of the Korean War, everyone worried some about teen-agers with cars and too much money.

Drinking was a growing problem among adolescents and school dropouts were a concern.

Five years ago, the man on the street would

From a talk given to the Sacramento County Medical Society, 6 April 1968.

Submitted 17 October 1968.

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have been startled by the news that "reefers," as they then were called, were actually being used by a few high school students.

How long ago that all seems now. Suddenly it was nineteen hundred sixty-three and one day in November an orange flame spurted from an upper-story window in the Texas School Book Repository in Dallas. The world began to change. A man accused of assassination was himself assassinated on national television . . . live. Day after day, the mournful line filed slowly past the catafalque while endless dirges filled the airways of radio and television.

In the days and years that followed, the process of change gathered momentum. Troop commitments climbed in Vietnam. The promise of "just one more escalation" seemed somehow never to be fulfilled. The good fellowship and optimistic dedication of the Selma March days of the civil rights movement gave way to political disillusionment, riots, militancy, and violence. Sit-ins by the Free Speech Movement staggered the administrative control of the University of California at Berkeley, and on campuses across the nation angry students watched, gained inspiration, and began to seek their own kind of confrontation. Overnight a quiet neighborhood near the intersection of Haight and Ashbury Streets in San Francisco became transformed into a street carnival of psychedelic sights and sounds. The "Summer of Love" drew 100,000 children to its crowded streets and, failing, gave way to the winter of discontent, leaving a residue of hard core drug users to corrupt the hippie ethic with crime, defiance, and sexual excess. On the Sunset Strip in Los Angeles, in Greenwich Village, in Denver and in a dozen or more major cities across the United States, the drop-out ghettoes came into being almost simultaneously and pursued their garish course toward drugs, love and disease.

Indeed the past five years are a bewildering kaleidoscope of the artifacts and appurtenances of a youthful and uncertain social revolution, more far-reaching perhaps than any the world has yet known. Acid, rock, Timothy Leary, light shows, Bob Dylan, grass, speed, underground newspapers, The Sexual Freedom League, gurus, Stop the Draft Week . . . these are the flames of a firestorm of change, coming faster almost than the mind can cope with them, challenging old values, tempting, outraging, disturbing, yet touching something meaningful in young and old alike.

The Hippie World

Suburbia was, of course, in some degree of trouble as a place for rearing children years before the hippies came along. Growing up in the hothouse atmosphere of middle class affluence, never wanting for anything, with parents whose successful careers and busy social lives left them less time than there needs to be for family matters, without much in the way of formal religious training or any kind of stable value system, the teen-agers of suburbia have gradually become over the past two decades more "spoiled," more lacking in motivation, and more easily led into delinquent acts than other young populations have been.

When the Haight-Ashbury, Sunset Strip and other meccas of the hippie world suddenly sprang into existence in 1965 and 1966, they were only an easy hitchhike down the highway from Suburbia, and restless teen-agers soon found their way and began to make the scene on weekends and after school with regularity. There was a great deal about this that was disturbing for parents and community leaders, but one of the more upsetting developments had to do with drug usage. Stories began to circulate. Could it be that as many as 10 percent were using drugs in some high schools? That was shocking. Something should be done.

Nothing was, however. Time went on and some of the adolescents disappeared into the hippie world altogether. The ones who commuted back and forth to Suburbia brought back the culture with them—more drugs, posters, long hair, and a jumble of philosophical concepts that sometimes didn't withstand logical analysis but nevertheless contained a core of truth that made them surprisingly satisfying and difficult for the older generation to refute.

Marijuana in High School

One should not, of course, overestimate the influence of this process of subversion of the adolescent. On the grounds of suburban high schools, there are still to be seen, at least to the casual glance, throngs of bright, laughing, conventionally-clad youngsters carrying books, chattering, and exploring the mysteries of male and female just as they have always done. But the undercurrents are there too, unmistakable, for one who would see them: a few kids in hippie clothes, a "joint" passed quickly but with surprising openness from hand to hand in the parking lot. Peace and Freedom Party posters, and a hundred other indications that something is stirring.

A recent issue of a California high school newspaper[1] published the results of a survey conducted by the students themselves to determine the extent and nature of marijuana use. Nearly 1,800 boys and girls, three-fourths of the student body, responded to the questionnaire 45 percent, (806) reported that they had tried marijuana, and 31 percent, (554) indicated that they continued to use the drug. Usage, as might be expected, increased sharply from lower to upper classes, and among the graduating class 57 percent stated that they had experimented with marijuana and 45 percent said that they continued to do so. In response to one interesting item, "Which constitutes the greatest threat to your health following excessive use?", 44 percent answered alcohol, 37 percent nicotine, only 13 percent marijuana, and 6 percent caffeine.

And the Other Mind-Altering Drugs

The survey did not inquire into the use of mind-altering agents other than marijuana. The impression of those who work closely with problems of drug usage is that the taking of LSD has diminished decidedly in recent months. The rash of bad trips and publicity about chromosome damage has made the adolescent far more wary of this substance than he once was; and, together with more stringent laws, higher prices, and relative unavailability of a trustworthy supply on the market following several recent arrests of large scale manufacturers, this has made LSD something that is more likely to be used, if at all, by college students rather than high school youngsters. At any rate, those who want to progress beyond marijuana nowadays are more likely to turn to amphetamines. "Crystal" or "speed" is readily obtainable; and the "trip," with its sense of increased rate of thinking and heightened motor powers, is probably inherently more appealing to the children of our success-oriented computer culture than the more introspective and mystically-oriented counterpart journey with "acid." Ironically, speed seems to make the teen-agers feel for a few hours as if, perhaps after all, they can measure up to the standards of their parents, which they reject consciously but unconsciously still desire to fulfill.

While the teen-agers of Suburbia drift from drug to drug in search of euphoric escape from a world they suddenly find unacceptable, their parents, for the most part, stand by bewildered and uncomprehending. Having little actual contact with the phenomenon except through frightening newspaper headlines and from anecdotal knowledge of tragic cases that have occurred among children of their friends and acquaintances, adults concoct from their own unfulfilled desires and projected fears a terrifying concept of what is going on that leaves them in a state of panic and paralysis. In their minds, it is as if the Pied Piper of Hamelin has gone through the country, blowing "weed." And where he has been, the children have followed: first a trickle, then a rivulet, then a stream, then a torrent and a flood until in the minds of parents the danger is everywhere and the children are truly lost. They can do little except wail, wonder what they have done wrong, and hold conferences and plan programs that somehow do not help.

Surely this nightmare, conjured up from the murkiness of the unconscious minds of the World War II generation, which has somehow now so bewilderingly found itself failing at everything it turns its hand to, is an exaggerated view of the menace of drugs. But what would be a more accurate appraisal and how are we really to measure what we are up against and plan sensibly?

An Appraisal of the Problem

Probably it is fair to say that the most irrational fears, which hold that we are raising a generation of drug addicts are unfounded. For one thing, the only background against which we can judge current events, our only concept of the drug user, is the black-and-white characterization of the "dope fiend" publicized by the Federal Bureau of Narcotics in the 1930s and '40s and such a concept equips us poorly to understand what is going on now. For another, the drug that is most widely used, marijuana, has not been clearly shown to be harmful and may not be as widely destructive as we fear. LSD and the amphetamines are another matter but harm that stems from their usage, while more clearly predictable, is still confined to a relatively small number.

However, if the risk to the entire generation is perhaps not immediate and overwhelming, the risk to individuals is often very real. This is particularly true for youngsters whose past experiences and uncertain ego development have brought them to adolescence more insecure and more vulnerable than their peers. In the author's private practice, for example, during the year 1964, none of the teen-agers seen were involved with drugs; but, in contrast, during 1967 every young patient had used drugs to some extent and more than three-fourths were seriously committed to the daily employment of drugs and to the culture of the drug world.

Whatever the final outcome of the current furor over marijuana and other drugs may be, it does at least seem clear by now, after two to three years of experience, that the unrestricted and indiscriminate use of mind-altering agents and total immersion in the underworld of drug use are poor adjuncts to psychotherapy. Psychiatrists over and over again have seen disturbed adolescents begin to make some progress toward understanding and controlling themselves only to abandon it all to the seductions of acting-out, hippie-style, and lose the gains they have made. Furthermore, in addition to interfering with psychotherapy, it is clear that the opportunity that drugs and the drug culture provide for repeated escape is a poor kind of developmental experience for troubled adolescents. In private practice, in clinics and on the wards of state hospitals, one sees increasingly the casualties—young boys and girls whose lives have been blighted, perhaps beyond recovery, by drug-accelerated psychopathology. To be sure, some of these would have lost out in life anyway and in time would have found some other medium like alcohol or psychopathic behavior for the expression of their unhappiness and inadequacy; but there is the impression that the number of the damaged has undergone a real increase under the blandishments of the drugs and the false promises of those who make the use of them a way of life.

The Importance of Facing Reality

Development is not an easy task at any level and it is particularly difficult for the adolescent in a complex society like ours. The task of hammering out a solid sense of identity requires courage and perseverance. There are many hurts and disappointments to be experienced along the way but the slow and painful work of building a self must never be abandoned. It does not help the adolescent to have ready-made ways of giving up or of avoiding the challenges of his life, yet this is what the drugs seem fundamentally to provide. The greatest harm that they do comes from the fact that, although the drug itself may not be habituating, the experience of easy escape and rationalization is and very quickly becomes a way of life from which, paradoxically, there is no escape.

However, even if it is true that some number of children who might otherwise have rescued themselves from the toils of adolescent turmoil will be sucked under and lost, still one senses, after all, that the majority will either never become involved seriously or will find their way back from the edge of the quicksand. From the standpoint of the individual there will be all too many tragedies, but from the standpoint of society the cost in grossly damaged lives may not in the end be too great.

The Responsibility of Adults

There is reason, however, to be concerned at a deeper level than this about effects that are more subtle and more far-reaching. The young people say, “Let us alone, let us take drugs, let us do our own thing—we’re not hurting anyone.” Indeed there is some truth in what they say, for one must truly strain to find evidence that their “thing,” in and of itself, is causing enough gross damage to society to warrant its prohibition, at any cost and on a society-wide scale, if in fact such were possible. But each generation, ours included, has a right and an obligation to take seriously its stewardship of the world for those few short years when positions of power pass into the hands of its members and when years of experience bring to it at least the potential for wisdom. To abdicate that right is perhaps just as wrong as is the imposition of a dictatorship of age over the young.

We as physicians are members of an adult generation. We and our contemporaries, more than the young generation, are in a position to think seriously about the long range effects of a drug culture on the worlds of today and tomorrow. We have a responsibility to face questions that only we can face, because we have, unlike the young, seen more than one generation and have some sense of where time can lead. We must ask, because no one else can or will, the serious questions: What will be the real and lasting effects on the generation of the young for their adolescent experience to have been so deeply colored by the easy availability of pharmacologically induced thrill and escape? What kind of people will they grow up to be, where will their values come from, where will they find the motivation, what sorts of adults will they really make when they are suddenly, irrevocably over 30?

Another kind of concern is not so much for the future and what will become of the adolescent as it is for the present and what will happen to adults because of the drug problem and related issues. This is not to suggest that adults are likely very quickly to abandon the social customs that have been built up over the years around the consumption of alcohol and switch to another intoxicant. That seems relatively unlikely if for no other reason than that of cultural inertia. But the drug problem exerts other kinds of pressures than the urge to change. One of the most deleterious of these is the effect of unanswered accusations. It is not psychologically healthy for a generation to have thrust upon it in anger and defiance wave upon wave of issues and questions that undermine its own sense of continuity with the past and destroy its confidence in the capacities that it has acquired just at the moment in time when those capacities are most needed by the world. To be endlessly beleaguered like this, without answer and with diminishing self respect, is to be robbed of the most fruitful and satisfying period of life; rather than submit in confusion to such an impeachment, the adult generation would do well to turn all of its resources toward the understanding and solution of each of the problems that plague the world, be they drug usage, international aggression, civil rights, overpopulation or any other.

The Physician's Special Role

In this larger sense, the problem of drug abuse belongs to all of society, and resolution of the problem will require the efforts of far more than just the physicians. But there are aspects of the problem where physicians are uniquely qualified and can contribute skill and knowledge that no other profession offers. There is an immediate and imperative need for research, for instance, and for laws that facilitate the gathering of information about drugs and their effects on the human organism and human lives. To know so little about something that has suddenly become so important is to grope in the dark at a time when the next step is critical and light is most needed. Physicians can support and participate in both laboratory and clinical research and, through their medical societies, have an opportunity to represent forcefully the need for reappraisal of the rules and regulations that now make it virtually impossible for scientists to obtain supplies of marijuana and LSD for study and experimentation. Such restrictions do little to protect society from abuse and, on the other hand, do much to deprive it of vitally needed knowledge.

Another aspect of the drug abuse problem has to do with a growing dependency of the general population on medications of various sorts as a solution to difficulties and symptoms, particularly those having to do with tension and its physical and psychological manifestations. Physicians, especially those who are involved in medical education, need to engage in a searching reexamination of the whole philosophy of contemporary medical practice and the degree to which it inadvertently fosters such dependency. At the same time attention needs to be paid to the mounting commercialism of the pharmaceutical industry, to the perhaps excessive and injudicious use of advertising and to the enigma of the modern drug house which seemingly must utilize hard sell methods and push an endless stream of new products in order to survive in the competitive world of business enterprise yet periodically justifies these questionable means by producing, because it has been able to sustain itself and to grow, therapeutic innovations that are truly life saving and miraculous.

The Need for Information

An obvious need bears on education. Physicians need to educate themselves, their patients and, participating in organized programs of various kinds, the children and parents of their community. There is a great demand for the immediate dissemination of all available information regarding drugs and their psychological and physiological effects, the nature of habituation and addiction, and the social and psychological conditions that predispose to the use of drugs.

The federal and state laws pertaining to marijuana and other drugs are under increasing attack. It is alleged that they are unduly punitive and that they are not soundly based on medical and scientific fact.[2] As in the days of Prohibition, accepted practice is diverging more and more widely from the dictates of the law, and the law does not receive the respect that is necessary for it to be the cornerstone of stability in the community. As the current limits on drug usage are questioned, there is a tendency to question other limits on behavior as well, and the situation edges more and more toward a condition of license which is bewildering and seductive to the young adolescent faced with his first difficult choices with regard to drugs. Physicians can help in this area by examining the medical basis for current legislation, by urging their reevaluation if that seems indicated, by contributing valid knowledge and information to any rehearing that may take place, and by supporting to their fullest, along with the rest of society, whatever statutes result.

In any aspect of the drug problem in which he becomes involved, be it research, community education, clinical contact with patients, or legislative endeavor, the physician will make a more meaningful contribution if he approaches his work with an open mind and with a willingness to learn. He should not abandon the responsibilities of his knowledge and maturity because of the emotional pressures of the moment, but at the same time he should try not to be blinded by prejudices of the past. We need to educate the youth today, but perhaps first we need to educate ourselves and become able ourselves to be free to change. Basically, as in any learning process, it will not be so much the facts that will be absorbed by young people as it will be the manner in which we face the problem and conduct ourselves in trying to deal with it. If we can find ways of approaching this question and others with honesty, industry and intellectual integrity, then we will have conveyed something by example that can be truly valuable.

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TREATMENT OF DISSEMINATED CHORIOCARCINOMA

"We have used a variety of regimens and a variety of drugs for women with disseminated choriocarcinoma. Up to the present time, we've found only two drugs to be outstandingly effective — Methotrexate and actinomycin D.

"In the use of Methotrexate, we've found that we obtain our best results in a regimen which gives Methotrexate by continuous infusion and at the same time gives the patient twice daily folinic acid. This is a complex process. It can be argued that it ought to eliminate the therapeutic effect of Methotrexate completely. But we are able to judge the effect by the excretion of chorionic gonadotropin in these tumors; and in fact, we observed better response with this Methotrexate-folinic acid regimen than we have with either Methotrexate alone or with Methotrexate and 6-mercaptopurine. Its big advantage is that it reduces the level of toxicity. . . . The patient does not suffer severe stomatitis. She does not suffer severe hair loss. She still gets some degree of hematopoietic depression. These are important savings. There is a very much reduced mortality rate from toxicity; we've had no deaths in patients treated in this way. A high proportion — something like 50 percent — of the patients are apparently cured by this Methotrexate-folinic acid regimen. If they don't respond to this, then we have to go into actinomycin. We have no way of reducing actinomycin toxicity; but if the patient has been treated in the first place with this Methotrexate-folinic acid regimen, the toxic effects are very much better contended with than if the patient has already had several months of Methotrexate treatment in the conventional way."

—KENNETH D. BAGSHAWE, M.D., London
Extracted from *Audio-Digest Internal Medicine,* Vol. 15, No. 23, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

CASE REPORTS

Hereditary Elliptocytosis With Hemolytic Anemia—A Family Study of Five Affected Members

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HEREDITARY ELLIPTOCYTOSIS is an uncommon disorder in which the majority of circulating erythrocytes are elliptical or oval. It is inherited as an autosomal dominant. While most persons with hereditary elliptocytosis are asymptomatic, approximately 12 percent of them show evidence of increased hemolysis.[1] Hereditary elliptocytosis with overt hemolytic anemia is quite rare.[2] However, it is particularly important to establish the diagnosis, since splenectomy will correct the hemolytic anemia.

This report describes a 40-year-old Caucasian woman who had many of the complications associated with chronic hemolytic anemia. The patient and her four children were found to have hereditary elliptocytosis and were studied extensively. Certain biochemical similarities between hereditary elliptocytosis and hereditary spherocytosis are illustrated.

Reports of Cases

Case 1. The patient, a 40-year-old Caucasian woman, first learned of being anemic in 1955 when, during a stay in hospital for a ruptured ovarian cyst, a hemolytic episode developed. This was associated with clinical jaundice, dark urine and rapidly developing anemia requiring transfusions.

Approximately two years later she had a second hemolytic episode, which was associated with viral pneumonia. Between these episodes she was well and unaware of being anemic or jaundiced. She had no known family history of anemia.

She was admitted to the Hawthorne Memorial Hospital in March 1967 because of symptoms of biliary tract disease. X-ray studies showed evidence of cholecystolithiasis. At the time of admission she appeared slightly icteric. The spleen was enlarged to 6 cm below the left costal margin and the liver to 5 cm below the right costal margin. There were no other significant abnormal physical findings.

Hemoglobin was 9.4 grams per 100 ml of blood, the hematocrit 28 percent, and reticulocyte count 8.9 percent. Approximately 50 percent of the circulating erythrocytes were elliptical. Oval spherocytes were noted on the peripheral blood smear as

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This investigation was supported by USPHS Research Grant HE-08757 from the National Heart Institute.

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Submitted, revised, 21 October 1968.

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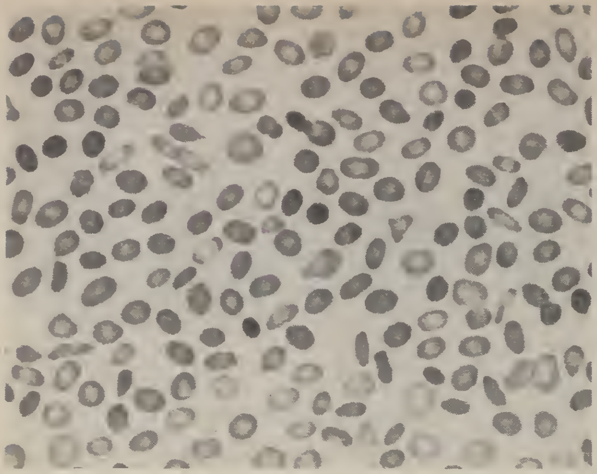

Figure 1.—Photomicrograph of peripheral blood smear in Case 1 (before splenectomy). There is a moderate degree of elliptocytosis and a tendency to spherocytosis. An occasional irregularly shaped red cell is also present. × 400

well as an occasional typical spherocyte. A few irregularly shaped red cells were also present (Figure 1). Leukocytes numbered 10,000 per cu mm with normal differential count. Platelets were normal. The bilirubin was 3.2 mg per 100 ml, of which 2.8 mg were indirect. Tests of liver function were otherwise within normal limits. The Coombs test was negative.

A diagnosis of hemolytic anemia due to hereditary elliptocytosis was made and the patient was studied at the Hematology Research Laboratory at Harbor General Hospital. Routine and special hematological studies and enzyme assays were performed according to previously published methods,[3,4] except for aldolase (modification of Wu and Racker by Schrier[5]). The results of hematological and biochemical tests are summarized in Tables 1, 2, and 3. The autohemolysis test (Table 2) was clearly abnormal; the increased hemolysis was corrected by glucose as well as by adenosine and adenosine triphosphate. The osmotic fragility was normal with fresh red cells, but abnormal with red cells incubated for 24 hours at 37°C (Chart 1).

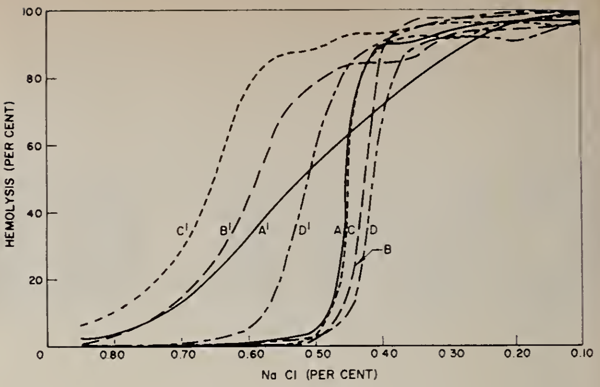

Chart 1.— Osmotic fragility curves of fresh and incubated red cells. A, A^1=Case 1, fresh and after incubation; B, B^1=Case 2; C, C^1=Case 3; D, D^1=normal control. The pattern of Case 4 and Case 5 was similar to that of Case 3. Note that in all patients the osmatic fragility of incubated red cells is increased.

The results of the red cell enzyme assays (Table 3) indicated either normal or increased activity before splenectomy (consistent with a young mean cell age) and a decrease to normal levels after splenectomy when the hemolytic process had been corrected. However, it is to be noted that the acetylcholinesterase activity remained elevated. Aldolase activity was normal.

On 27 April 1967 splenectomy and cholecystectomy were performed. The spleen was congested and weighed 550 grams. The gall bladder contained numerous bilirubinate calculi. No transfusions were necessary. Post-operatively, the hematocrit rose rapidly to normal levels with a concomitant decrease in reticulocyte count to normal

TABLE 1.—*Clinical and Hematologic Data on Propositus (Case 1) and Her Children*

Data	*Case 1 (Propositus)* *Before Splenectomy*	*Case 1 (Propositus)* *After Splenectomy*	*Case 2 (Son)* *Before Splenectomy*	*Case 2 (Son)* *After Splenectomy*	*Case 3 (Daughter)*	*Case 4 (Son)*	*Case 5 (Daughter)*
Age	40		18		22	16	5
Sex	F		M		F	M	F
History of anemia	+		—		—	—	—
History of jaundice	+		—		—	—	—
Palpable spleen	+		+		—	—	—
Spleen weight (gm)	550		552		. .	. .	. .
Hemoglobin (gm per 100 ml)	10.1	15.2	14.2	14.7	13.5	15.8	11.8
Hematocrit (%)	28	43	37	46	35	40	32
Erythrocytes (10^6 per cu mm)	3.32	5.23	4.98	. .	4.35	5.25	4.35
Reticulocytes (%)	16.2	2.0	8.6	1.3	4.7	4.4	5.1
Leukocytes (per cu mm)	4318	7629	3676	. .	5974	4565	3656
Osmotic fragility							
Fresh cells	Normal		Normal		Normal	Normal	Normal
Incubated cells	Increased		Increased		Increased	Increased	Increased

TABLE 2.—*Results of Autohemolysis Studies in Propositus (Case 1) and Her Children*

Additive *Compound*	*Final Conc.*	*Normal Mean*	*Case 1 (Propositus)* *Before Splenectomy*	*After Splenectomy*	*Case 2 (Son)*	*Case 3 (Daughter)*	*Case 4 (Son)*	*Case 5 (Daughter)*
None	..	1.7	15.6	13.3	18.0	12.5	10.3	14.9
Glucose	.026 M	0.2	1.6	.5	.2	.6	.2	.3
Adenosine	.02 M	0.2	1.1	.4	.3	.8	.6	.7
Adenosine Triphosphate	.02 M	0.2	.5	.3	1.0	1.3	.3	.6

The percent hemolysis in the patients is the average of the values obtained in duplicate bottles at 48 hours.

levels. The postsplenectomy blood smear demonstrated a slightly greater number of irregularly shaped erythrocytes than before splenectomy. There was no significant change in the degree of elliptocytosis. The patient was restudied at Harbor General Hospital approximately four months after splenectomy (Tables 1, 2, and 3).

Case 2. The patient, an 18-year-old son of the patient in Case 1, had always considered himself to be in good health, but on questioning admitted to some degree of easy fatigability and occasional aching pain in the left upper quadrant of the abdomen. On examination the spleen was observed to be enlarged to 2 cm below the left costal margin. Hemoglobin was 12.2 grams per 100 ml of blood, the hematocrit 37 percent. The peripheral blood smear demonstrated the presence of elliptocytes. The reticulocyte count was 4 percent. Special studies (Tables 1 and 2 and Figure 1) were then performed. Autohemolysis and osmotic fragility tests demonstrated abnormalities similar to those of his mother. Red cell aldolase activity was 2.96 (see Table 3 for normal range and units).

On 25 August 1967, splenectomy was performed. The spleen weighed 552 grams and appeared congested. The patient had an uneventful post-operative recovery. Three months after splenectomy, hemoglobin was 14.7 grams, hematocrit 46 percent and reticulocyte count 1.3 percent. The patient noted a definite improvement in feeling of well-being, and disappearance of chronic fatigue.

The other three patients (Cases 3, 4, and 5) are also children of the patient in Case 1. All of these children were asymptomatic, and none had palpable splenomegaly. However, on peripheral blood smears all had elliptocytes morphologically similar to those of Cases 1 and 2. Their hematological values are summarized in Table 1. All had an elevated reticulocyte count and were slightly anemic. The red cells of all three demonstrated an abnormal autohemolysis test similar in pattern to that of their mother (Case 1) and sibling (Case 2) (Table 2). The osmotic fragility of incubated red cells was increased in all three of these children. A representative result (Case 3) is shown in Figure 2. The red cell aldolase activity in Cases 3, 4, and 5 was 2.56, 2.45, and 2.67, respectively (see Table 3 for normal range and units).

Discussion

The five patients presented herein had evidence of hemolytic disease. All had a variable degree of anemia, reticulocytosis and elliptical red blood cells. Two patients (Cases 1 and 2) had palpable splenomegaly. The propositus (Case 1) had major complications of hemolytic disease. She had at

TABLE 3.—*Red Blood Cell Enzymes in Case 1*

Enzyme	*Case 1 (Propositus)* *Before Splenectomy*	*After Splenectomy*	*Normal Range*
Acetylcholinesterase	116	121	90 - 110
Glucose-6-phosphate dehydrogenase	5.78	3.80	2.55 - 3.89
6-phosphogluconate dehydrogenase	3.67	2.70	1.84 - 3.04
Glutathione reductase	3.05	.....	1.70 - 3.80
Phosphofructokinase	6.92	.....	5.12 - 7.46
Hexokinase	0.69	0.24	.11 - .33
Aldolase	3.47	2.65	1.71 - 2.47
Triosephosphate isomerase	435	220	173 - 263
Glyceraldehyde-3-phosphate dehydrogenase	31.1	.....	24 - 45
Phosphoglycerate kinase	45.8	.....	35 - 58
Pyruvate kinase	10.53	.....	4.03 - 6.93
Glutathione	672	783	683 -1311

The units are micromoles of di or triphosphopyridine nucleotide oxidized or reduced per minute per 10^{10} erythrocytes at 37°C, except for acetylcholinesterase expressed as percent of normal and glutathione expressed as micrograms per 10^{10} red cells.

least two episodes of accelerated hemolysis and had symptoms of chronic, recurrent gall bladder disease. The patient in Case 2 complained of fatigue and occasionally of pain in the region of the spleen. Both of these patients had splenectomy, followed promptly by resolution of the hemolytic process.

Hereditary elliptocytosis is usually discovered as an incidental finding at the time of routine blood smear examination. The peripheral blood smear reveals oval or elliptical erythrocytes. There is no agreement in the literature about the diagnostic criteria of elliptocytosis, but the presence of greater than 25 percent elliptocytes is generally considered a requirement for diagnosing hereditary elliptocytosis.[6] The incidence of hereditary elliptocytosis has been estimated at four cases per 10,000 population in the United States.[7] It is generally agreed that cases of hereditary elliptocytosis fall into three groups: (1) those with no signs of hemolysis, (2) those with compensated hemolysis, and (3) those with non-compensated hemolysis.[2] The relative frequency of the three categories is not yet definitely known. The majority of persons who have the condition are totally asymptomatic and routine laboratory tests fail to reveal evidence of hemolysis. From a review of the literature up to 1943, Penfold and Lipscomb[1] estimated that some degree of increased red blood cell destruction was present in approximately 12 percent of cases. However, in a recent extensive study utilizing more sophisticated methods, Geerdink and associates[6] demonstrated that elliptocytosis as a rule caused compensated hemolysis. The patients may be asymptomatic or may note mild, vague symptoms of malaise and abdominal pain as seen in Case 2 of this report. On the other hand, an occasional patient (such as the one in Case 1) may have moderate to severe anemia and is prone to the usual complications of chronic hemolytic disease.

Hereditary elliptocytosis is inherited as an autosomal dominant,[2] as is illustrated in the family reported herein. The disorder may be detected at birth[9] and may be the cause of significant neonatal morbidity.[8,10] During the course of the disease patients may have exacerbations of anemia due to hemolytic crisis or from temporary bone marrow failure or folic acid deficiency with megaloblastosis.[9] Overt hemolysis may become manifest for the first time as the result of stressful situations such as surgical operation or intercurrent infection as illustrated by our Case 1. Cholecystolithiasis is common.[2,9] Patients showing a significant degree of hemolysis usually, but not invariably, have palpable splenomegaly and may have symptoms referable to this enlargement.

Dacie[2] states that there is no clear relationship between the degree of elliptocytosis and the presence or absence of hemolysis. It is usually emphasized that the elliptocytosis is as pronounced in cases without obvious hemolysis as in those with overt evidence of hemolysis.[2,11] However, Cutting and coworkers,[8] after reviewing published photographs of smears and their own cases, suggested that in the hemolytic cases oval forms predominate and often the abnormality is compounded by the presence of spherocytes and fragmented forms. This description characterizes the morphologic features of red cells of the five patients with hemolysis described herein. On the other hand, decided elliptocytosis with rod forms would be less likely to be associated with hemolysis according to Cutting.[8] This morphologic picture has been seen in this hospital in a 91-year-old man with a normal hemoglobin level and no evidence of hemolysis by routine studies. In addition, his red cell acetylcholinesterase activity, fresh and incubated osmotic fragility, and autohemolysis were normal. Our limited observations would thus support the viewpoint of Cutting and his associates.[8]

Our studies and those of other investigators[2,9,11] suggest that in general the pattern of osmotic fragility and autohemolysis tests differ between persons with no evidence of overt hemolysis and those with overt hemolysis. In the former category, the osmotic fragility (both fresh and incubated) and autohemolysis tests are normal. In the group with evidence of hemolysis, the osmotic fragility of fresh blood is usually normal, but may be increased, and that of incubated blood is almost always increased. Autohemolysis is increased in persons with evidence of hemolysis, and is corrected by the addition of glucose, adenosine or adenosine triphosphate. Thus, the pattern of these studies is similar to that of hereditary spherocytosis.[2,12,13]

At present, no specific biochemical defect has been recognized as characteristic of elliptocytosis. The glycolytic intermediates of fresh red cells are normal, but De Gruchy and coworkers[11] noted on incubation a more rapid than normal fall in adenosine triphosphate and 2,3 diphosphoglycerate and a more rapid rise in inorganic phosphate. All of the enzymes in the glycolytic pathway were normal n a patient reported by Cutting and coworkers.[8] No abnormalities were detected in red cell enzyme studies in our Case 1. The increased activity of several enzymes before splenectomy in that patient s consistent with a young mean red cell age before splenectomy. Red cell aldolase was at the upper border of normal or increased in all five of our patients. This enzyme was assayed particularly because of certain biochemical similarities between hereditary elliptocytosis and hereditary spherocytosis and because a deficiency of aldolase in hereditary spherocytosis has been suggested recently,[14] though aldolase activity has been considered to be normal in this disease.[13]

It is likely that in hereditary elliptocytosis, as n hereditary spherocytosis, passage through the spleen "stresses" the red cell, bringing to light the metabolic defect, which in the absence of the spleen remains clinically latent.[11] It is of interest that increased osmotic fragility and a higher bilirubin level have been noted in splenic venous blood compared with that of peripheral venous samples in hereditary elliptocytosis.[15]

Hereditary elliptocytosis patients with overt hemolysis respond favorably to splenectomy,[2,8] as was illustrated by our two patients who had the operation. As in hereditary spherocytosis, splenectomy for hereditary elliptocytosis corrects only the increased erythrocyte destruction. The genetically determined elliptocytes persist after splenectomy, as do the abnormal results of osmotic fragility and autohemolysis tests. In our Case 1 there was no significant change in the autohemolysis test after splenectomy, in contrast to a rise reported in a patient treated by Davidson and Strauss.[15] The persistence of the elevated red cell acetylcholinesterase, a membrane enzyme, after splenectomy in Case 1 is similar in pattern to that of patients with hereditary spherocytosis studied in our laboratory.

Splenectomy is not indicated in patients with hereditary elliptocytosis who have no signs of hemolysis. In patients with non-compensated hemolysis the condition is readily diagnosed and they should have splenectomy. It is in the group with compensated hemolysis that the disease is usually asymptomatic and may escape detection. However, once the diagnosis is established, it would appear reasonable that splenectomy should be performed if there is no concurrent condition that would significantly increase the surgical risk. These patients, although not anemic, run an increased risk of developing problems related to the rapid turnover of red blood cells. Some of these patients may also be unaware of the subtle, vague symptoms produced by the presence of a chronic hemolytic process until it is rectified. Because of the reported increased incidence of severe infections in children after splenectomy, elective operation should be withheld in mild cases until after the first few years of life.[16]

Summary

Five cases of hereditary elliptocytosis with hemolytic disease in one family are presented. One member had moderately severe anemia with complications related to the hemolytic process. Splenectomy in this patient as well as in one of her four children with mild anemia resulted in clinical cure. Certain biochemical similarities between hereditary elliptocytosis with evidence of hemolysis and hereditary spherocytosis are illustrated in this family study.

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Attempted Suicide by Cyanide

A Report of Two Cases

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EXCEPT FOR EXPOSURE to the agent in industrial settings most cases of serious cyanide intoxication encountered in the United States are from ingestion with suicidal intent. The clinical manifestations of cyanide intoxication appear within seconds to minutes of exposure. They include giddiness, hyperpnea, headache, palpitations, cyanosis and unconsciousness, with asphyxial convulsions preceding death.[1] Despite the widespread notion that ingestion of large amounts of cyanide is quickly and invariably fatal, there is ample evidence that as long as the heart beats, specific therapy for cyanide poisoning is almost always effective.[2] Two near-fatal cases of attempted suicide with cyanide are presented which illustrate the importance of the odor of the breath and the electrocardiographic changes in diagnosis, and also emphasize the duration of survival before therapy. They are presented as dramatic reminders of the necessity for having the appropriate antidote on hand in all facilities where emergencies or accident are dealt with.

Reports of Cases

Case 1. A 22-year-old single white man, a chemical engineering student, collapsed on the sidewalk and was brought to the Cambridge (Mass.) City Hospital emergency room by the Cambridge Emergency Rescue Service. Respirations were slow, deep and stertorous. The face was flushed, the skin of normal turgor and texture. The pulse was full and irregular and the pupils widely dilated without response to light. There was no evidence of recent head trauma. The chest was clear, and the heart tones were of good quality. No abnormality of abdomen or genitalia was noted. There were scattered fresh abrasions on the right knee and shin. Deep tendon reflexes could not be evoked, and there was no response to deep pain or plantar stimulation.

Because ingestion of a toxic substance was suspected, endotracheal intubation with a cuffed tube was attempted in preparation for gastric lavage. On the first attempt to pass the tube, the patient vomited large quantities of dark orange material which had the characteristic pungent odor usually likened to that of bitter almonds. Simultaneously, a suicide note was found in the patient's pocket, and cyanide poisoning was suspected. Subsequently, a cuffed endotracheal tube was positioned in the trachea and ventilation with 100 percent oxygen by Ambu bag, with amyl nitrite ampules held over the intake valve, was carried out. A large gastric tube was passed and the stomach was washed with 3 liters of normal saline solution.

A cardiac monitor showed an abnormal QRS pattern with pronounced ST elevation and shortening of the QT interval. A standard electrocardiogram confirmed these abnormalities and also recorded an irregular rhythm at 60-70 without P waves.

Ten ml of 3 percent sodium nitrite solution from the Cyanide Poisoning Kit (Lilly) were drawn up into a syringe for intravenous administration. The estimated interval from cyanide ingestion to intravenous nitrite administration was 20 minutes. Before the injection, no blood pressure was obtainable, although a pulse remained palpable in a femoral artery. After 7 ml had been given the patient became pulseless, and external cardiac massage was immediately begun. Ten ml of a 1:10,000 solution of aqueous epinephrine was administered intravenously, and a strong pulse at 180 beats per minute was obtained after 2 minutes of external cardiac massage. Sodium thiosulfate, 50 ml of a 25 percent solution, was next given intravenously, and as cyanosis began to fade the patient began to move his extremities and to blink his eyes. Within a few minutes, the pulse and blood pressure stabilized, but mental status did not improve further and he remained unresponsive to verbal stimuli. A repeat course of nitrite-thiosulfate treatment was therefore begun, after which cyanosis cleared completely and the patient sat up and looked about. He then began to cough up copious amounts of pink frothy sputum through the endotracheal tube. It was not certain whether this resulted from acute cardiac failure due to cyanide intoxication or

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Submitted 4 November 1968.

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was from pulmonary edema caused by chemical irritation from aspirated stomach contents. Dexamethasone was given, 8 mg intravenously, and two ampules of 50 percent mannitol (25.0 grams), as a dehydrating agent both for the possible acute congestive failure and possible cerebral edema due to cerebral anoxia. Within 15 minutes, coughing subsided. An x-ray film of the chest showed a normal heart and fluffy infiltrates; this cleared in 14 hours.

The patient later related that he and his fiancee had argued by phone, after which he took a test tube containing about 1.5 grams of sodium cyanide, which he had been carrying for several months, poured it into a cup of coffee, drank it, left the house immediately, and collapsed on the sidewalk.

The patient was seen by psychiatrists from his University Health Service, who diagnosed a schizoaffective disorder, and he was discharged to a private mental hospital 19 hours after arriving in the emergency room. Physical examination, laboratary studies, chest x-ray film and electrocardiogram were normal before discharge. Six months later there were no abnormalities on an electroencephalogram, and results of psychological testing were normal.

Case 2. A 24-year-old white woman, a laboratory technician, was brought by police from home to the Accident Floor of Mt. Auburn Hospital, Cambridge. She was said to have had "tetanics" at home, apparently trismus with respiratory distress, followed by collapse and a possible seizure during the half hour preceding admission. She had no history of previous seizures or syncope and had had generally good health except for episodes of depression.

On arrival, she was comatose, the extremities were flaccid and deep tendon reflexes were absent. No blood pressure was obtainable and the femoral pulse was weak, at 110 beats a minute. Respirations were irregular at 6 to 10 a minute, and a rectal temperature was 99.6°F. The pupils were dilated and unresponsive to light. There were no signs of head trauma, and the neck was supple. The mucous membranes were slightly cyanotic and moist without ulcerations or enanthem. A "bitter almond" odor was detected on the patient's breath. The skin was cool and dry with piloerection and diffuse mottling. Except that heart sounds were distant, the chest, abdomen and extremities were within normal limits.

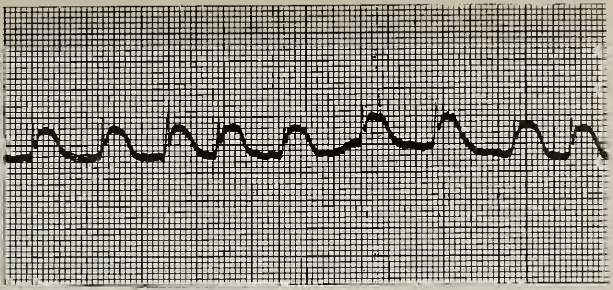

Figure 1.—In Case 2, the AVF lead showed atrial fibrillation, ectopic ventricular beats and an abnormal QRS with the T wave beginning high on the R wave.

An electrocardiogram showed a normal sinus rhythm initially, with subsequent atrial fibrillation, occasional ectopic ventricular beats, and an abnormal QRS with the T wave originating high on the R wave (Figure 1).

Ventilation with 100 percent oxygen was carried out through a cuffed endotracheal tube. The stomach was washed with several liters of saline solution after a nasogastric tube had returned a small amount of light colored, viscid secretions. The blood pressure was supported at 100 to 120 mm of mercury with intravenous metaraminol. Because of the suspicion of acute cyanide intoxication, 10 ml of a 3 percent sodium nitrite solution was given intravenously over a 4-minute period, then 17.5 grams of sodium thiosulfate. (Both agents were obtained from a Lilly Cyanide Kit.)

Immediately following the injection of sodium nitrite and thiosulfate, the patient became moderately cyanotic, and cyanosis cleared over the next 15 minutes. She made no spontaneous movements for roughly 5 minutes following the nitrite-thiosulfate administration, but by the end of 15 minutes she had regained consciousness and was able to state that she had taken cyanide to kill herself. The vital signs stablized, metaraminol was discontinued, and she was taken to the Intensive Care Unit for further observation.

Subsequently it was learned that she had made two previous attempts at suicide, once by ingesting Clinitest® tablets and once by inhaling cooking gas. On the present occasion, she took one teaspoonful of potassium cyanide granules (4 to 6 grams) in a tumbler of water about 25 minutes before arriving on the Accident Floor. She had obtained the potassium cyanide from the laboratory in which she worked. The approximate time between ingestion of cyanide and treatment with sodium nitrite was 50 minutes. Recovery was uneventful, with prompt reversion of the electrocardiogram to normal. There were no pathological neurologic sequelae. The patient was returned to the care of a psychiatrist who had treated her previously.

Discussion

The odor of hydrocyanic acid (HCN) released into the air from solutions of sodium or potassium cyanide is readily detected, even in small concentrations, by most observers. The smell and the taste of HCN have a characteristic musty quality that resembles that of bitter almonds or macaroons. Although the odor of cyanide on the breath and in the vomitus is an immensely important sign of cyanide poisoning, it has been known for over 50 years that some persons are insensitive to this odor. Gwilt[3] estimated that 20 to 40 percent of all people are unable to detect cyanide by odor, a figure which was not altered by laboratory training. Kirk and Stanhouse demonstrated that 24 of 132 males and 5 of 112 females studied were unable to distinguish a 20 percent solution of potassium cyanide (KCN) from distilled water; they found the ability to smell KCN related to a sex-linked recessive gene.[4]

Although in the present cases the diagnosis of cyanide intoxication was made on the basis of the odor of cyanide, electrocardiograms provided corroboration. The increase in amplitude of the T waves, progressive ST segment shortening, and eventual origin of the T wave high on the R wave were seen in both cases. These changes resemble those seen within 10 minutes of exposure to lethal concentrations of HCN gas reported by Wexler.[5] Ingestion of cyanide is not necessarily quickly fatal; in most of the 24 cases of recovery from severe cyanide poisoning (reported by Chen[6]) the patients were attended to within 2 to 20 minutes of exposure, but four were not first treated until 90 to 150 minutes had elapsed. The fatal dose of KCN in adults is estimated to be 200 to 250 mg,[7] although Liebowitz[8] reported a case of complete recovery, without specific therapy, following a dose of 3 to 5 grams of KCN.

The pharmacologic rationale for treatment of cyanide intoxication with sodium nitrite and sodium thiosulfate, described by Chen and Rose, depends on the production of methemoglobin, which competitively binds CN^- and removes it from cytochrome oxidase, thus alleviating the fatal block of cytochrome function and permitting formation of cyanomethemoglobin. The cyanide attached to the hemoglobin is then converted to the nontoxic thiocyanate by the administration of sodium thiosulfate, due to the existence of a specific enzyme, rhodanase. In man, the intravenous injection of 0.6 grams of sodium nitrite results in a maximum methemoglobin concentration of about 17.5 percent,[9] cyanosis becoming apparent at a level of about 15 percent. Since levels of 30 percent methemoglobin do not usually produce significant symptoms, and the lethal dose of sodium nitrite for man is about 2 grams,[10] it is apparent that a dose of 0.3 to 0.6 grams of sodium nitrite is well within safe limits.

With rational and safe therapy commercially available, it appears that continued success in the treatment of non-occupational cyanide intoxication resides primarily in the continued education of physicians to suspect the diagnosis (particularly in young, depressed persons with access to chemical compounds) and to have at hand a supply of antidotes.* Unless he is one of those persons who cannot detect it, the characteristic odor of cyanide will be easily recalled by a physician if he troubles to acquaint himself with it.

Summary

In two cases of attempted suicide by ingestion of cyanide, the classic odor of cyanide and electrocardiographic changes led to prompt diagnosis. Both patients were treated successfully with sodium nitrite and sodium thiosulfate from commercially available cyanide antidote kits.

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*Cyanide antidote kits are available containing pearls of amyl nitrite, ampules of sodium nitrite (0.3 grams in 10 ml of water), and ampules of sodium thiosulfate (12.5 grams in 50 ml of water); the contents of these kits have been demonstrated to be stable for up to 29 years.

Metabolic Bone Disease Secondary To Renal and Intestinal Disorders

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■ *Metabolic bone disease occurring in renal or intestinal disorders has been reviewed with particular reference to etiological factors.*

Hyperparathyroidism *is seen as a recurring cycle of renal damage—hyperphosphatemia—hypocalcemia—parathyroid stimulation—mobilization of bone calcium and phosphate—renal tubular phosphate rejection. In intestinal cases, the initial stimulus is presumably hypocalcemia.*

Osteomalacia *is seen as resulting from phosphate depletion for the following reasons:*

1. *Experimentally, rickets results from dietary phosphate restriction in rats.*
2. *Such rickets is not prevented by the presence of normally adequate amounts of dietary vitamin D, and may therefore be termed "resistant" in the clinical sense.*
3. *Osteomalacia or rickets in intestinal malabsorption and renal tubular disorders is associated with hypophosphatemia due to excessive fecal or urinary loss.*
4. *Renal tubular rickets has been healed by oral phosphate loading in some studies.*
5. *Acidosis may induce osteomalacic changes, experimentally and clinically (for example, in uretero-sigmoidostomy). Reversal of systemic acidosis with oral bicarbonate has resulted in phosphate retention and a rising serum phosphate in one such case.*
6. *Preliminary data from analysis of* full-thickness *bone biopsy in two osteomalacic patients shows a significant reduction in calcium and phosphate content.*
7. *Despite the hyperphosphatemia of azotemic renal failure, over-all phosphate depletion may be present in this situation also due to:*
   - *Diminished dietary phosphate in low protein diets*
   - *Nausea and vomiting*
   - *Occasional diarrhea*
   - *The use of oral phosphate-binding antacids*
   - *Perpetuation of urinary phosphate losses by reduction in proportion of tubular reabsorbed phosphate (secondary hyperparathyroidism) and possibly high filtered load per nephron*
   - *Repeated losses of phosphate to bath fluid during dialysis.*

METABOLIC DISEASE OF bone is a common occurrence in renal disease and in disorders of intestinal absorption. The clinical manifestations may be minimal, absent, or severe. The pathogenesis of these various derangements in bone metabolism has recently attracted considerable attention not only because of clinical importance but because of the wider implications concerning the variables which normally control osteogenesis and osteolysis—secretion and activity of parathormone and thyrocalcitonin, vitamin D (its ingestion, absorption and conversion to metabolites of altered biological activity), the varying contributions of calcium, magnesium, and phosphate and the modifying effects of steroidal hormones.

The subject of renal osteodystrophy was reviewed in 1967 by Stanbury[1] in Britain and Kleeman and his colleagues[2] in the United States. Very recently a conference on divalent ion metabolism in chronic renal failure[3] provided additional data. A comparable recent review of the osteodystrophy of intestinal origin is not, however, available, and in particular a survey of points of similarity or difference in the etiologic lineage of the two conditions may be of some interest at the present time.

Bone disease in intestinal malabsorption and renal disease, both tubular and glomerular, may present either as osteitis fibrosa generalisata due to secondary hyperparathyroidism or as osteomalacia. Occasionally, a third lesion—hyperostosis—may be seen, particularly in renal cases.

A fourth disease entity, osteoporosis, is at the same time so difficult of definition and so commonly suspected in any over-fifty age group that no attempt will be made in this review to associate it specifically with renal failure or malabsorption. It should be noted, however, that Garner and Ball,[4] on the basis of semi-quantitative histological measurements, suggested that a reduction in "bone mass" or osteoporosis is a feature of malabsorptive cases, whereas an increased bone mass is seen in chronic renal disease.

Osteitis Fibrosa Generalisata

The diagnosis of hyperparathyroid bone disease is made from the characteristic radiological appearance of sub-periosteal erosions in the phalanges (Figure 1); microscopic evidence of osteitis fibrosa in a bone biopsy (Figure 2); and measurement of increased plasma parathormone levels.[5] This lesion is commonly seen in renal failure[1,2] and its incidence appears to increase with maintenance dialysis.[6] Doubtless the true incidence is greater than suggested by radiological evidence alone, and could better be assessed *in vivo* by routine bone biopsy studies. Follis and Jackson[7] and Berner[8] showed osteitis fibrosa in one-third of renal failure cases at autopsy. All who have measured serum parathormone levels in uremic patients agree that very high values are the rule.[5,9,10] Reiss and coworkers[10] have further shown significant elevation of serum levels at the stage of minimal renal damage (creatinine clearance 70-80 ml per minute).

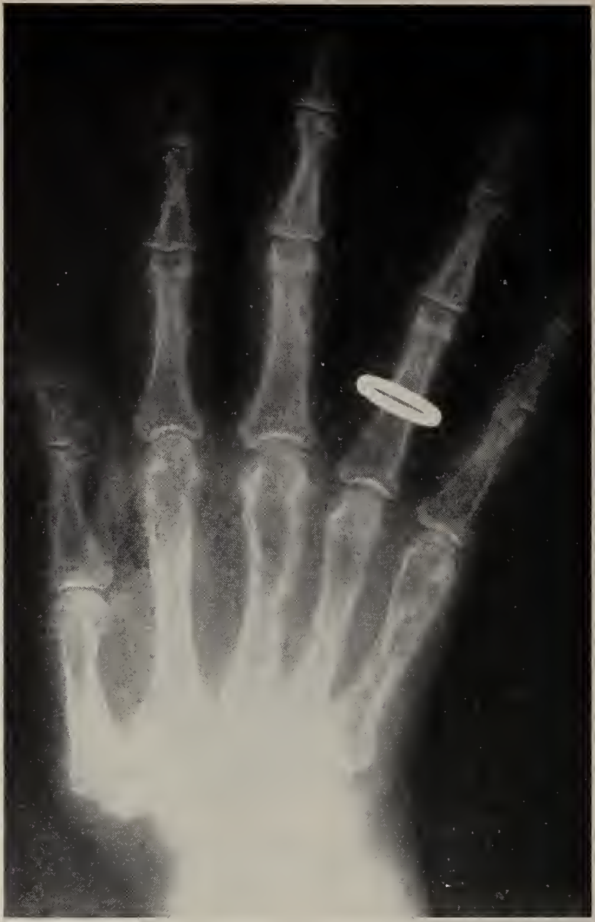

Figure 1.—Pronounced generalized rarefaction and subperiosteal erosion of phalanges in patient with renal failure and hyperparathyroidism.

By contrast, gross evidence of hyperparathyroid bone disease is much less common in intestinal malabsorption[11,12] in which osteomalacia is the predominant bone lesion. Reiss (during discussion at Santa Barbara meeting[10]) has stated that serum

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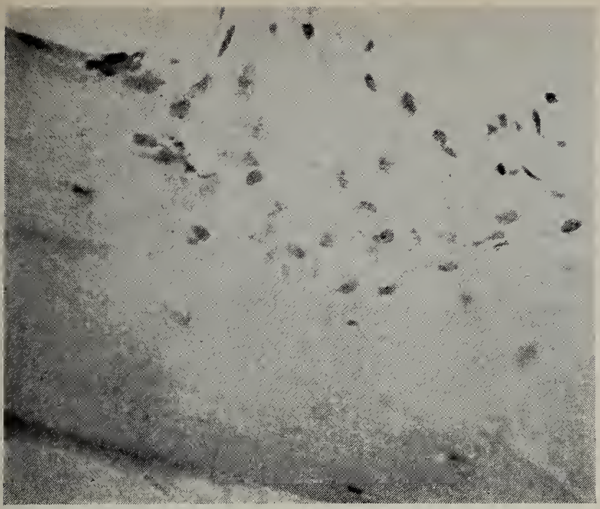

Figure 2.—Osteoclastic resorption in osteitis fibrosa generalisata (decalcified section).

parathormone values are raised, but not to the levels seen in uremia. This is in accord with the results of calcium infusion in such cases[13] which indicate an initial moderate reduction in percent tubular reabsorbed phosphate (TRP) with rapid reversal to normal following elevation of serum calcium. A corresponding degree of parathyroid suppression in the renal tubular syndrome of "hypophosphatemic rickets" may require much larger amounts of intravenous calcium.[14] Certain patients in both the renal and the intestinal groups, however, present with florid evidence of excess parathormone production described as "autonomous" or "tertiary" hyperparathyroidism. Such patients show well-marked radiological and histological osteitis fibrosa with hypercalcemia and metastatic calcification. Though well recognized in both intestinal[11] and renal cases[15] some time ago, it has become a more frequent problem with the advent of maintenance dialysis programs[6] and commonly requires parathyroidectomy. Whether the syndrome represents truly autonomous function or merely the effect of enormously hypertrophied parathyroid glands with correspondingly sluggish turn-off has been debated at length.[6,9,10] The consensus (based on the results of very large calcium infusions) favors the latter view, and this is supported by the finding that hypercalcemia following transplantation tends to regress spontaneously toward normal over a period of months.[16]

Davies, Dent and Watson[17] reviewed their experience of "tertiary" hyperparathyroidism recently. A surprising feature was the emergence of steatorrhea (commonly following gastrectomy) as a common associated disease in the majority of their subjects. The possibility of an underlying primary hyperparathyroidism, with associated peptic ulcer leading to gastrectomy, cannot be absolutely excluded in such cases, in which the diagnosis of "tertiary" disease rests heavily on the *late* appearance of hypercalcemia. A similar diagnostic difficulty is commonly encountered in renal cases, where hypercalcemia, nephrocalcinosis and uremia may be either the cause or the result of excess parathormone secretion. Fortunately, the recommended treatment (parathyroidectomy) appears the same for both primary and "tertiary" disease.

It seems probable that the stimulus for excessive parathormone secretion or secondary hyperparathyroidism is a fall in serum calcium. This would result in intestinal cases from malabsorption of calcium and vitamin D.[18] In renal cases it may be seen as induced by the physico-chemical effect of a rise in serum phosphate as glomerular filtration falls. Slatopolsky and coworkers[19] suggested that the latter is a step-wise progression with further compensatory parathormone secretion as glomerular filtration reduces. Stanbury and Lumb[20] questioned the role of rising serum phosphate levels, since no significant negative correlation was apparent between serum phosphate and calcium levels in their uremic cases. Kleeman and coworkers[2] contested this view and showed a marginally significant inverse relationship when correction was made for the unusually high fraction of "bound" calcium in renal failure. More significant, however, is the multiplicity of evidence that *acute* alterations in serum phosphate effect an inverse change in serum calcium.[21] This phenomenon is well preserved even in end-stage renal failure, as shown by the hypocalcemia following oral phosphate loading in the data of Liu and Chu[22] in 1942. Stanbury[1] later reviewed the evidence that experimental hyperparathyroidism in animals may be induced by feeding a high phosphorus diet with low calcium:phosphate ratio. Very recently, Aurbach and Potts[9] showed that a rise in serum phosphate levels *per se* does not affect parathyroid hormone secretion in cows, except insofar as serum calcium concentration may have fallen during this maneuver. The evidence therefore is highly suggestive that hyperparathyroidism in renal failure may be initiated and sustained by hyperphosphatemia acting via a reduced serum calcium concentration. The relative lack of prominence of osteitis fibrosa in intestinal malabsorption might be explained by the occurrence of hypophosphatemia rather than hyperphosphatemia in this disorder.

Additional reasons for persistent hypocalcemia in uremic patients are apparent failure of compensatory absorption of calcium from the gut and failure of the "calcemic" effect of circulating parathormone—both factors being apparently secondary to the state of "vitamin D resistance" which will be discussed below. These factors may be of particular importance in some chronic renal failure patients, in whom stable hypocalcemia is sometimes seen with little or no elevation of serum phosphate.[1,2]

Certain other factors possibly affecting parathormone secretion are also worthy of consideration at this point. Serum magnesium levels may be important in that hypermagnesemia certainly depresses parathormone secretion experimentally[23,24] although the converse experiment of perfusing the gland with hypomagnesemic fluid has not been reported. Raisz[25] commented on the necessity for considering the effects of serum ionized calcium plus magnesium rather than calcium alone, on hormone synthesis. We have recently studied the effect of replenishing magnesium deficiency in chronic steatorrhea cases.[26] This allows an interesting comparison with renal failure, in that hypocalcemia with secondary hyperparathyroidism is found in both situations, but serum magnesium levels tend to fall rather than rise in the former. Two main points of interest emerge: (1) Severe magnesium depletion is associated with profound hypocalcemia (serum calcium 4.5-5 mg percent) with additional evidence of "failure of parathyroid response" in that elevation of serum alkaline phosphatase and renal phosphate clearance were *not* seen and bone disease was completely absent (both radiologically and on biopsy). (2) Magnesium replenishment (Chart 1) was followed immediately by elevation of serum calcium, renal phosphate clearance, and sometimes serum alkaline phosphatase. The results do not distinguish between (a) failure of parathormone secretion, and (b) peripheral tissue unresponsiveness to circulating parathormone during magnesium deficiency.[25] However, a normal phosphaturic response to exogenous parathyroid extract[26] indicated that the first explanation may be preferred. Clearly measurements of serum parathormone levels before and after magnesium repletion are necessary to resolve the question. Occasional cases of hypomagnesemia may also occur in renal failure due to a magnesium-wasting syndrome, and Kleeman and coworkers[2] recorded one such case with severe hypocalcemia in which magnesium replenishment resulted in a significant rise in serum calcium. Alfrey and Jenkins[27] recently described a similar result in a patient with apparent tubular magnesium wasting without uremia.

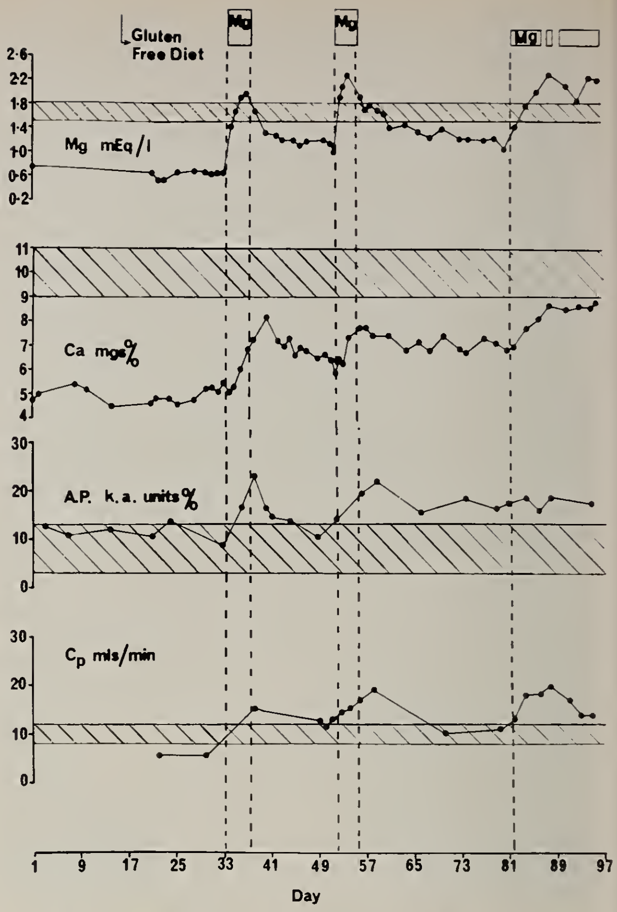

Chart 1.—Effect of intramuscular magnesium replenishment in three stages (vertical dotted lines) on serum magnesium, calcium, alkaline phosphatase (A.P.), and renal phosphate clearance in subject with steatorrhea, magnesium deficiency, and "functional hypoparathryroidism."

A possible effect of changes in extracellular fluid (ECF) or intravascular fluid volume on parathormone secretion should be considered in view of some recent, though admittedly tenuous, evidence connecting them. Epstein[28] reviewed the considerable evidence that urinary sodium and calcium excretion are directly related and concluded that daily urinary calcium rises with ECF volume expansion and falls with volume contraction. In this way the effect of chronic thiazide administration in reducing urine calcium was seen as an effect

TABLE 1.—*Change in Total Exchangeable Sodium ($\Delta\ NA_E$) in Hypertensive Subjects during Long-Term Diuretic Therapy*

Diuretic	*No. of Subjects*	*Dose*	*Duration (weeks)*	$\Delta\ NA_E$ *(mEq)*
Chlorthalidone	4	100 mg alternate days	4- 6	—395
Furosemide	9	40 mg twice a day	4- 6	—419
Chlorthalidone	4	100 mg alternate days	8-15	—245
Furosemide	9	40 mg twice a day	10-15	—229

of body sodium depletion. Recently an additional effect of chronic thiazide therapy has appeared[29] in that serum calcium has tended to rise with continued therapy. This phenomenon was confirmed in dogs, associated with a significant increase in weight of the parathyroid glands, at autopsy. The pattern of response of serum calcium which rose initially, returned towards normal after some weeks, and rose again only on increasing the diuretic dosage, is reminiscent of the temporary fall followed by later restoration of total exchangeable sodium during long-term furosemide studies in moderately hypertensive subjects as summarized in Table 1 (unpublished data). Interpretation of these findings must remain largely speculative at present. Clearly, however, careful serum calcium determinations are desirable during chronic diuretic administration in hypertension, cardiac or renal disease. In addition, observation of serum parathormone levels throughout the development of renal failure might profitably be correlated with changes in total exchangeable sodium or blood volume.

In summary, the radiological, pathological, and biochemical evidence of osteitis fibrosa in intestinal and renal disease has been confirmed by measurements of plasma levels of parathormone. The stimulus for parathyroid hyperplasia appears to be hypocalcemia. This probably results from hyperphosphatemia in azotemic cases, and from intestinal malabsorption of calcium and vitamin D in intestinal disease. Extracellular fluid volume depletion may be an additional factor. Inhibition of secondary hyperparathyroidism appears to result from magnesium depletion, either by inhibition of hormone secretion or by decreasing peripheral hormonal action on bone. Bone resorption may also be decreased by excess thyrocalcitonin and phosphate concentrations, as judged by *in vitro* studies.[25]

Osteomalacia

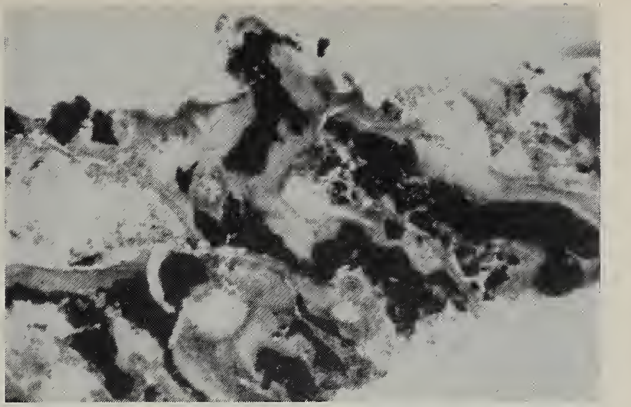

Figure 3.—Undecalcified iliac crest biopsy (Von Kossa stain) in patient with hypophosphatemic rickets. Note wide non-calcified osteoid seams surrounding black areas of mineralized bone.

Osteomalacia or rickets may be defined as failure of bone matrix mineralization. This is normally documented as excess non-calcified osteoid in a bone biopsy specimen.[30] (Figure 3) In approximately 50 percent of patients dying of renal failure, there is autopsy evidence of osteomalacia.[7,8] The diagnosis in intestinal or renal cases is initially suspected from symptoms of bone pain or from the charactertistic abnormalities in serum chemical contents, with calcium slightly low or normal, phosphate low (except in uremia) and alkaline phosphatase high. Restoration of such abnormalities to normal following therapy with vitamin D has been accepted as proof of the original diagnosis[31-33] in cases where bone biopsy has not been performed. Radiological changes may sometimes be nonspecific with an appearance of "generalized rarefaction," but the appearance of pseudo-fractures in scapulae, spinous processes, pubic rami or femora (see Figure 4) is pathognomonic of the disease. X-ray appearances are valuable in excluding Paget's disease, which in certain phases of activity may mimic osteomalacia both in histological sections (showing wide osteoid seams) and in serum chemical abnormalities.

In theory, osteomalacia might be caused by deficiency of (a) calcium, (b) phosphate, (c) alkaline phosphatase, or (d) vitamin D. Hypophosphatasia may be dismissed, since serum levels of alkaline phosphatase are high rather than low in the bone disorders under consideration. Depletion of calcium has been shown experimentally to result in osteoporosis rather than rickets or osteomalacia.[42,43] The remainder of this section will therefore be devoted to consideration of abnormalities of vitamin D or of phosphate or of both

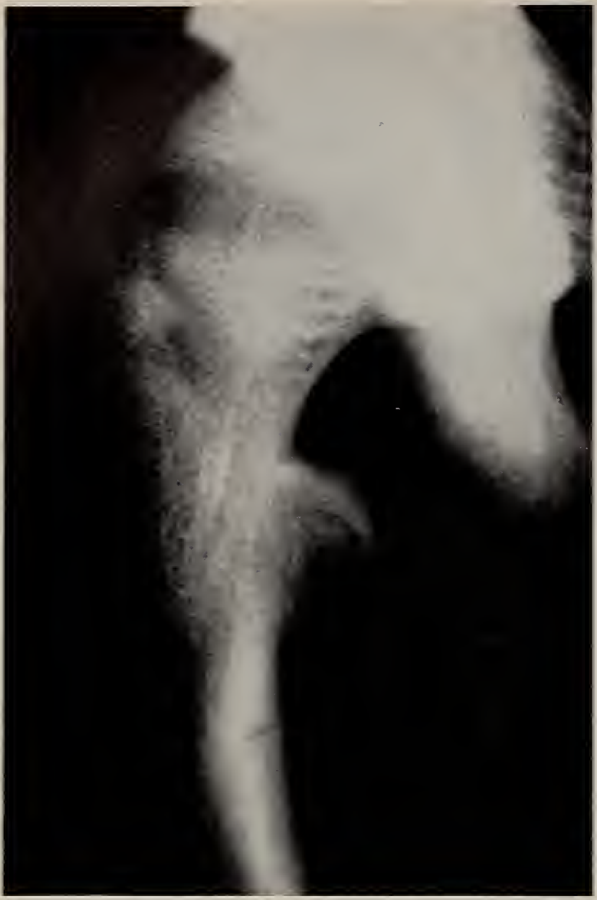

Figure 4.—Roentgenogram of femoral neck in patient (same as in Figure 3) with hypophosphatemic rickets. Psuedo-fracture is visible below lesser trochanter associated paradoxically with suggestive osteosclerosis in femoral shaft.

as etiological factors, with particular reference to the over-all importance of phosphate depletion.

Vitamin D Resistance in Osteomalacia

Perhaps the most sensitive index of vitamin D deficiency is provided by bioassay of serum antirachitic activity, which may in some post-gastrectomy cases indicate clinical vitamin D deficiency in the absence of demonstrable abnormality on bone biopsy.[32] In azotemic osteomalacia, however, plasma vitamin levels may be misleading, since Lumb, Stanbury and Wood[34] have shown that inadequate doses of vitamin D may restore plasma levels to higher than normal values without reversal of the bone disease process.

There is general agreement that the osteomalacia of both intestinal and renal disease requires much larger doses of vitamin D than are necessary in simple dietary deficiency rickets in children or adults.[1,22,35,36] The comparative dose requirements are approximately 100,000 to 400,000 units versus 400 international units of calciferol (though in individual renal cases healing may require as little as 40,000 or as much as 1,000,000 units). Lumb, Stanbury, and Wood[34] showed that simple intestinal malabsorption of orally administered vitamin is not the basis of this "resistance" in renal cases since plasma levels of many times normal values (as determined by biological assay) were sometimes associated with no detectable *in vivo* effect during metabolic studies. In intestinal cases, however, the studies of Thompson, Lewis and Booth[18] indicate that malabsorption of vitamin D is at least partly responsible for the "resistant" state.

The first definite evidence of an abnormality in the metabolism of vitamin D was provided recently by DeLuca and by Avioli and their colleagues.[37-41] The normal metabolism of the vitamin (probably in the liver) yields among their metabolites a particularly interesting product, 25-hydroxycholecalciferol, which apparently stimulates calcium transport in the duodenal slice preparation more quickly and to a greater extent than calciferol. Thus, following intravenous administration the time lag of intestinal activity was 6 to 10 hours with calciferol and 3 hours with active metabolite; and comparison of biological activity in rats and chicks showed a ratio of 1.4 to 1 in favor of 25-hydroxycholecalciferol[38] (previously designated as Peak 4 in chromatographic studies). A further point of interest is the ability of this metabolite to induce bone resorption in culture, whereas little or no effect was visible with calciferol.

Avioli[39-41] compared the metabolism of labelled calciferol in "vitamin D-resistant rickets" and chronic renal failure patients with the pattern shown in normal subjects. Whereas absorption from the gut appeared similar, subsequent fractional turnover was accelerated, with a higher proportion of radioactivity appearing in biologically inactive metabolites. This abnormality was unaffected by hemodialysis, but reversed by renal homotransplantation. A parallel study in uremic rats suggested a decrease in concentration of both labelled calciferol and 25-hydroxycholecalciferol in gut and bone.

These studies do not at present provide a complete answer to the problem of vitamin D resistance as seen clinically. The factor of 1.4 given by DeLuca[38] for the ratio of biological activity of 25-hydroxycholecalciferol to the parent vitamin seems insignificant compared with the three orders of magnitude difference in dosage requirement between renal and simple deficiency osteomalacia. Further studies in relation to specific accumulation of biologically active metabolites in bone may help to resolve this discrepancy.

Finally, the apparently abnormal patterns of metabolism of labelled calciferol may conceivably be a result rather than the cause of an underlying metabolic disturbance. A possible example of such a state is seen in experimental phosphate-deficiency rickets in rats, which is resistant to physiological doses of vitamin D.[42,43]

The Role of Phosphate Depletion and Systemic Acidosis in Osteomalacia

The possible significance of systemic acidosis and of phosphate depletion may be considered together, since they appear directly related in a number of physiological and pathological situations. Indeed, it is difficult to separate their individual effects even under experimental conditions. Thus systemic acidosis is associated with diminished maximal tubular phosphate reabsorptive capacity (TmP) in renal tubular acidosis cases; and administration of alkali increases TmP with simultaneous healing of bone disease.[44] A similar effect of acidosis was seen in the studies of Lemann and coworkers[45] during NH_4Cl loading in normal subjects. Pronounced phosphaturia resulted, with immediate cessation on discontinuance of the acidifying regimen.*

Conversely, renal excretion of acid is normally increased by oral phosphate loading in direct proportion to the rising urinary phosphate. A systemic alkalosis may be induced in this way in normal subjects as seen in the carefully controlled study of Relman and coworkers.[46] This illustrates the difficulty of interpreting the results of treatment with phosphate therapy alone in the bone disease of renal tubular syndromes. Reversal of hypophosphatemia in this way would almost certainly be accompanied by at least a partial restoration of serum bicarbonate levels.

An interesting example of such an interplay is provided in Charts 2 and 3, illustrating the results of therapy with oral alkali only in a patient with osteomalacia and systemic acidosis following uretero-sigmoidostomy some years previously. Reversal of systemic acidosis (with serum bicarbonate rising from 14 to 24 mEq per liter) was accompanied by a progressively positive external phosphate balance, due to diminishing excretion in feces-cum-urine. Serum phosphate also showed a serial increase from 1.6 to 2.4 mg per 100 ml. Of considerable interest is the absence of a significant effect of alkali therapy on external *calcium* balance, contrasting with the later pattern during calciferol administration, when the expected positive balance of both calcium and phosphate was clearly seen. These results resemble those of Harrison[47] and of Parsons,[48] neither of whom could demonstrate a change to positive calcium balance during adequate alkali therapy in uretero-sigmoidostomy patients. Unfortunately, phosphate balance results were not recorded in these studies.

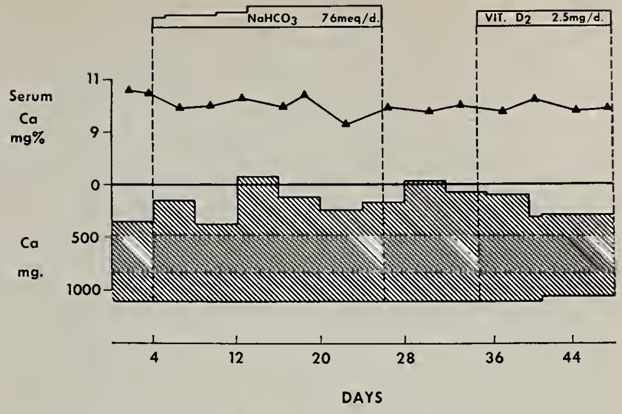

Chart 2.—Lack of effect of oral bicarbonate loading on serum calcium and external calcium balance in subject with severe acidosis and osteomalacia secondary to ureterosigmoidostomy. Intake is plotted down from zero line.

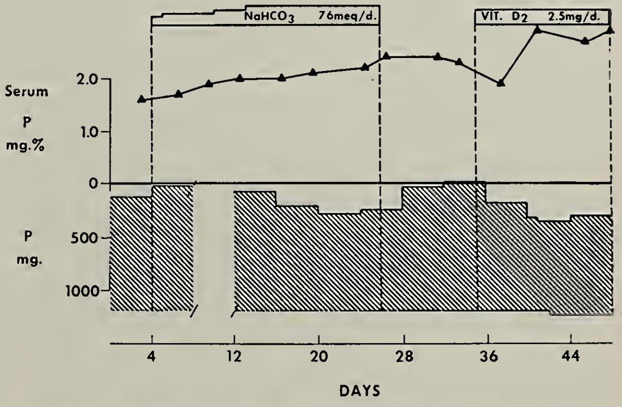

Chart 3. — Effect of oral bicarbonate loading on serum phosphate and external phosphate balance in subject (same as in Chart 2) with severe acidosis and osteomalacia secondary to ureterosigmoidostomy.

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*The immediate hyperphosphaturia and hypercalcuria resulting from this procedure was interpreted by the authors as an indirect effect of acidosis producing dissolution of bone salts. However, it should be noted that serum calcium and phosphate levels *fell* during this time, suggesting the alternative explanation that urinary losses may have represented a primary renal effect of NH_4Cl administration with a secondary effect on bone. Further study of the question, preferably with unilateral renal arterial acid infusion, seems desirable for fuller interpretation of these results.

The falling phosphate content in the pooled excreta of our patient could have been due to increased intestinal absorption or diminished renal excretion or both (glomerular filtration rate was 40 ml per minute measured by plasma disappearance of ^{51}Cr-EDTA). The data from the studies of Lemann and coworkers[45] and Dodge et al[44] quoted above, however, suggest strongly that a changing urinary excretion was responsible. Stanbury[1] also referred to unpublished observations in two patients with the "Fanconi syndrome" showing renal phosphate clearance rising during acidosis and falling during alkali therapy. Fecal excretion was not recorded.

The effect of alterations in acid-base balance on renal phosphate loss, as noted in these diverse circumstances, deserves emphasis in view of the common occurrence of acidosis in renal disease (both tubular and glomerular) and of the accumulating evidence that defective mineralization may result from deficiency of phosphate, rather than of calcium or vitamin D. It has been known for many years that rickets may be more readily induced experimentally by restricting phosphate rather than calcium intake. In addition both Coleman and coworkers[42] and Ferguson and Hartles[43] have shown that the development of phosphate-deficiency rickets in rats is unaffected by physiological doses of vitamin D and may therefore be termed "vitamin D resistant." The clinical counterpart of these experiments is seen in the ocurrence of osteomalacia in humans following oral ingestion of phosphate-binding antacids as described by Bloom and Flinchum[49] and by Lotz and coworkers.[50] A later metabolic study of experimental phosphate depletion in normal subjects by Lotz et al[51] documented a striking defense of body stores with almost complete disappearance of phosphate from the urine. The mechanism governing tubular phosphate reabsorption in these circumstances is therefore highly efficient.* It may not, however, be operative in the particualr situation of chronic renal failure, where continuing phosphaturia is maintained by a combination of hyperparathyroidism and high filtered load per surviving nephron.

There is no conceptual difficulty in suggesting that malabsorptive patients may lose excessive amounts of phosphate in the feces, or that renal tubular syndromes such as hypophosphatemic rickets may similarly become depleted as a result of "phosphate diabetes." In each case hypophosphatemia is a clear indication. The further evidence that phosphate administration may heal the osteomalacia of tubular syndromes has recently been reviewed by Arnstein and coworkers.[53] In azotemic renal disease, however, the presence of high serum phosphate concentrations has clouded the question, and indeed phosphate deficiency as a possible basis for the development of azotemic osteomalacia, has not received close attention in recent surveys of the disease. Failure to consider this aspect may perhaps be ascribed to a natural preoccupation with external *calcium* balance (see, for instance, the study of Harrison[47] cited above) or to the prominence given to the high serum phosphate levels and calcium-phosphate product of glomerular failure. Liu and Chu[22] for instance interpreted hyperphosphatemia as "indicating definite phosphate retention." This view is, however, considerably altered by the evidence that hyperphosphatemia is maintained at the expense of mobilization of bone salts under the influence of excess parathormone secretion with renal "retention" playing a minor (though initially important) role. Stanbury, Lumb and Nicholson[54] showed that parathyroidectomy in renal failure results in a *fall* in serum phosphate as well as calcium. This fall occurs despite a pronounced reduction in renal phosphate loss and is strongly suggestive of a reparative process by which bone salt is restored. Stanbury[1] has nevertheless discounted the phosphate depletion theory of renal osteodystrophy put forward by earlier workers, on the basis that fecal losses could not be documented (as required by the suggestion of Mitchell[55] that hyperphosphatemia induced loss of phosphate to the intestinal lumen). This argument does not, however, take into account the persisting urinary phosphate losses in uremia. Subsequently the studies of Slatopolsky and coworkers[19,56] have clearly outlined the importance of continuing parathyroid secretion as a stimulus to renal excretion of phosphate, even in the stage of advanced renal failure with grossly restricted GFR (for example, 3 ml per minute). Thus the absolute daily urinary excretion appears not significantly less than during normal renal function[56,57] due to the very decided reduction of TRP from 85 percent to less than 20 percent, as well as to the effect of hyperphosphatemia in maintaining a high filtered phosphate load per nephron. Since at the same time dietary phosphate intake is often reduced due to nausea, vomiting or the prescription of low protein diets, and diarrhea or phosphate-binding antacids may further aggravate intestinal losses, the stage seems set for the production of body phosphate depletion. An important addition to this chain of events would be the effect of chronic dialysis, causing further loss to the dialysing fluid—an intriguing possibility whereby the known higher incidence of osteodystrophy[6] may conceivably be explained in such patients.

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*There is a possibility that some degree of systemic alkalosis may have resulted from the extremely large doses of "non-absorbable" magnesium and aluminum hydroxides used in this study. Magnesium hydroxide is recognized to be partly absorbable and may raise urine pH.[52] The rapid diminution in urinary phosphate might conceivably be attributed to this factor, analogous to the effect of alkali in ureterosigmoidostomy osteomalacia and the Fanconi syndrome mentioned above.

How much does systemic acidosis contribute to continuing renal loss of phosphate? Neither Dent and coworkers[35] nor Stanbury and Lumb[20] found any significant effect of oral bicarbonate therapy on external calcium or phosphate balance (the period allowed for study was in general rather short, but at least in Cases 2 and 9 of Dent's study and Case 2 of Stanbury and Lumb, 18 to 30 days of therapy appeared ineffective). Dent and coworkers[35] were careful, however, to draw a distinction between patients with primary renal tubular defects and those with glomerular osteodystrophy in the pattern of response, noting that those with tubular defects appeared to be controlled on alkali therapy alone (no balance data being available). Our uretero-sigmoidostomy patient (Figure 4 and Chart 2) had a measured GFR of 40 ml per minute and was therefore more akin to the patients with tubular syndromes of acidosis and osteomalacia rather than to these authors' patients with advanced glomerular disease. It may be that tubular phosphate reabsorptive capacity (or resorption of bone mineral, or both) is unresponsive to pH change in the stage of advanced renal failure—due perhaps to the profound inhibition of TRP shown by Slatopolsky and coworkers[56] in this phase, or to the effect of a large filtered phosphate load per surviving nephron. This by no means excludes a possible phosphaturic effect of importance induced by acidosis during the *development* of renal disease. The results of Lemann and coworkers[45] in normal subjects are fully consistent with this hypothesis. Future studies of the effect of alkalis during the *early* stages of renal acidosis (GFR 20 to 40 ml per minute) are necessary to resolve the question.

Bone Biopsy Analysis

Unfortunately, the presence or absence of overall phosphate depletion is difficult to examine by conventional techniques in the particular situation of renal failure with osteodystrophy. Thus, whereas the results of parathyroidectomy clearly indicate phosphate-hungry bones, confirmation of diminished phosphate content is not forthcoming in the available published analyses of bone biopsy specimens. Kaye[59] analyzed the mineral composition of the fourth lumbar vertebra at autopsy in patients with suggestive radiological evidence of hyperostosis. Calcium and phosphate content in this selected group was shown to be elevated, expressed either per unit volume or unit weight of fat-free dry bone. These authors emphasized the possibility that analytical results based on obviously hyperostotic vertebrae might not be representative of the skeleton as a whole. Subsequently, Pellegrino and Biltz,[58] in an analysis of cortical bone biopsy specimens from rib and tibia of uremic patients, found some diminution in calcium with no change in phosphate content.

An important reservation in the interpretation of the results of Pellegrino and Biltz[58] was voiced by Stanbury[1] in pointing out that the data were derived from analysis of *cortical* bone only. In an attempt to study further the chemical composition of cancellous as well as cortical bone, we recently utilized the technique of Byers and Smith[60] in obtaining whole-thickness iliac crest biopsy specimens including outer cortex, cancellous bone and inner cortex. Table 2 cites preliminary results in two osteomalacic patients (one renal and the other malabsorptive in origin) compared with six autopsy specimens from apparently normal subjects. Whereas no diminution in calcium or phosphate content was seen when expressed per 100 grams of

TABLE 2.—*Analysis of Full-thickness Iliac Crest Bone Biopsy*

			Grams per 100 grams of bone ash		*Grams per 100 grams of fat-free dry bone*	
Subject	*Diagnosis*	*Histology*	*Ca*	*P*	*Ca*	*P*
Patient 1	Uremic Osteomalacia	Wide osteoid seams	36.3	17.4	15.7	7.60
Patient 2	Malabsorption Osteomalacia	Wide osteoid seams	35.9	20.9	11.9	6.95
Six normal subjects:						
Mean	——	——	36.3	16.73	22.4	10.32
S.D.			(0.52)	(0.175)	(1.38)	(0.498)

bone ash, the osteomalacic subjects showed an unequivocal reduction of 30 to 40 percent in both calcium and phosphate content expressed per kilogram of fat-free dry bone. This finding seems to fit exactly with the histological appearances of large areas of uncalcified osteoid in both subjects. Survey of the literature reveals no comparable data for whole-thickness (including cancellous) bone biopsy analysis in osteomalacia. If these preliminary observations are confirmed, the question must further be posed whether apparent bone mineral depletion results from negative external balance or from increased growth of osteoid creating a disproportion between mineral content and the reference base of "fat-free dry solid." The results of Kaye[59] and of Garner and Ball[4] would suggest the latter interpretation in the case of uremic osteodystrophy; in malabsorptive osteomalacia, the former mechanism may possibly be preferred.

Study of the available external metabolic balance data before therapy in uremic cases adds little to the proof or disproof of over-all phosphate depletion, since interpretation is strongly influenced by continuing secondary hyperparathyroidism, as discussed above. Oral phosphate loading studies such as those of Liu and Chu[22] are equally difficult to interpret since the resulting rise in serum phosphate and reciprocal fall in serum calcium apparently stimulates further parathormone secretion, with increased phosphaturia.

The remarkable absence of bone disease in magnesium-depleted subjects,[26] despite gross steatorrhea and hypocalcemia, deserves further comment at this point. Since the majority of these patients were normophosphatemic, with normal or low renal phosphate clearance, the first inference might be that the phosphate-sparing effect of a "functional hypoparathyroid" state had prevented the onset of osteomalacia. This explanation, however, is clearly invalid in the case of one of these patients in whom unpublished observations showed that *fecal* phosphate loss exceeded intake by 600 to 800 mg daily, and serum phosphate values were consistently less than 2.0 mg per 100 ml. An alternative explanation may be that the histological criterion of osteomalacia — excess uncalcified osteoid tissue — is dependent on the action of parathormone, either in the mobilization and transfer of bone salts or in the actual formation of osteoid. Stanbury[1] and Garner and Ball[4] have previously discussed this latter possibility, based on quite different inferences derived from histological appearances and animal and *in vitro* experimental data. Thus the action of parathormone may be important in the development of osteomalacia, and further in the formation of actual hyperostosis by virtue of a preliminary excess osteoid deposition. The coincidence of unexpected absence of osteomalacic changes with presumptive failure of secondary hyperparathyroidism in the magnesium depletion syndrome appears to provide further evidence in support of this concept.

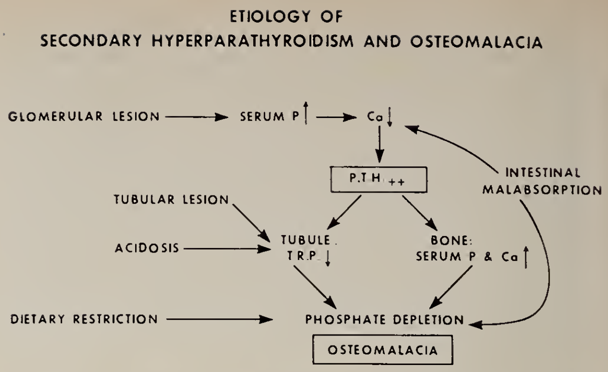

Chart 4.—Suggested temporal schema of events giving rise to metabolic bone disease in chronic renal disease (glomerular or tubular) and intestinal malabsorption.

In summary, the justification for placing emphasis on phosphate depletion, rather than lack of calcium or vitamin D, as an important etiological factor in the development of both intestinal and renal osteomalacia must rest on the established experimental evidence in rats, as well as the corroborative data in humans mentioned above. Thus calcium deprivation alone results in osteoporosis, whereas phosphate depletion results in rickets.[42,43] The failure of vitamin D in physiological doses to prevent rickets in the phosphate-deprived rats of Coleman and coworkers[42] and Ferguson and Hartles[43] is of key importance in this concept, and provides an experimental analogue of clinical vitamin D resistant rickets. In this way, vitamin D resistance may be seen as a consequence rather than the cause of the primary mineral disturbance. It would be most interesting to see if the abnormal vitamin D metabolism, so elegantly documented by Avioli[39-41] and DeLuca[37,38] in clinical disease, could be reproduced in these animals as a result of simple phosphate depletion.

Chart 4 illustrates in schematic form the suggested mode of development of both hyperparathyroidism and osteomalacia in glomerular lesions. The initiating stimulus to bone destruction is seen as transient phosphate retention with hyperphosphatemia, secondary reduction in serum calcium, parathyroid stimulation, followed by mobilization of bone calcium and phosphate, with tubular P rejection and phosphaturia. The two end results are (1) osteitis fibrosa, and (2) bone phosphate depletion and osteomalacia. This sequence of events has previously been suggested by Stanbury,[1] Kleeman and coworkers[2] and Slatopolsky et al[56] as far as the stage of development of osteitis fibrosa only. In primary (or apparently primary) tubular lesions, the initiating stimulus may be suggested to commence at the point of excessive phosphaturia (whether an intrinsic defect[61] or due to secondary hyperparathyroidism seems immaterial) leading to phosphate depletion and osteomalacia. In both situations the presence of acidosis may act as a potentiating phosphaturic stimulus, as discussed above. Diminution of phosphate intake by dieting or through nausea or therapy with phosphate-binding antacids would be additional factors.

In the case of intestinal malabsorption, bone disease is suggested as commencing with fecal phosphate loss leading to phosphate depletion, hypophosphatemia, and osteomalacia. This process is worsened by malabsorption of vitamin D.[18] The known predominating lesion of osteomalacia with relatively minor evidence of osteitis fibrosa in malabsorptive cases[12] is fully consistent with this theory.

Conversely, the development of osteomalacia might be delayed or even prevented by habitual *high* phosphate intake. One may speculate that this factor may be of importance in American subjects as compared with their Irish and British counterparts. Milk-drinking together with a high meat intake are established national customs in the United States where, in addition, each quart of milk is fortified with 400 units of vitamin D. This may conceivably explain the apparent difference in incidence of clinical renal osteomalacia, which is common in the British Isles but rare in the United States, where the picture of hyperparathyroid bone disease appears to predominate. Perhaps also a high phosphate intake may not only delay rachitic changes but positively stimulate the parathyroids, as suggested by the experimental production of osteitis fibrosa in animals.[62,63]

Differential Diagnosis of Underlying Lesion

A review of a clinical disease state such as metabolic bone disease may appropriately end with consideration of the difficulties of differential diagnosis and the management of an individual patient. The history and dietary survey of milk and butter intake will detect the currently rare patient with simple vitamin D deficiency osteomalacia. The condition is still seen sometimes in an elderly recluse living alone in poverty.[33] Further initial diagnostic steps are the exclusion of hypophosphatasia and uremia by appropriate measurements of serum chemical contents.

Alternatively, abnormal urine pH and serum bicarbonate values may indicate renal tubular acidosis, or a more widespread tubular dysfunction may be suggested by glycosuria, amino-aciduria and excessive phosphate clearance. These indices, however, do not necessarily establish the diagnosis of primary renal tubular disorder with secondary osteomalacia. Such a diagnosis is rare, with intestinal malabsorption (gluten enteropathy, postgastrectomy steatorrhea, blind loop syndromes) remaining much the commonest cause of malacic bone disease today. Unfortunately, small intestinal disorders may be relatively asymptomatic, as seen, for instance, in the recent follow-up study of adult subjects known to have had "celiac disease" in childhood.[66] It therefore becomes essential to exclude positively the presence of intestinal disease in all osteomalacic subjects, by means of quantitative fecal fat measurement and jejunal biopsy examination. This requirement has been emphasized by our recent finding that osteomalacia of both intestinal and dietary deficiency origins may be complicated by renal tubular disorders such as phosphaturia, renal tubular acidosis, and amino-aciduria.[33,65] These abnormalities appeared to develop as a result of secondary hyperparathyroidism, since they could be reversed temporarily by calcium infusion or by vitamin D therapy, and could be induced in certain circumstances by parathormone infusion. Such a temporary disorder is clearly not due to intrinsic renal tubular disease, but may nevertheless mimic this syndrome in its initial manifestation in the osteomalacic patient. For this reason, osteomalacic subjects presenting with apparent "Fanconi syndrome," "renal tubular acidosis," or "hypophosphatemic rickets" should be carefully screened for occult small bowel disease. In addition, a final diagnosis of "primary renal tubular disorder with osteomalacia" cannot be established until a trial of therapy with adequate doses of vitamin D has tested the possibility of reversible tubular dysfunction due to secondary hyperparathyroidism.

ACKNOWLEDGEMENTS

This review was written during the tenure of a visiting professorship in Dr. L. H. Smith's department. My thanks are due to Dr. Smith and Dr. G. S. Gordan for much stimulation and helpful criticism, and for advice on the manuscript. The data in Figures 6, and 7, Tables 1 and 2 and Chart 1 are derived from studies with Drs. T. J. McKenna, J. Donohue, and J. Healy, and Misses R. Freaney, M. Swan, and C. Kampff at University College and St. Vincent's Hospital, Dublin. I am indebted to Dr. R. P. Towers for the preparation of the bone biopsy material in Figure 3.

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CONTROL OF CHRONIC GRANULOCYTIC LEUKEMIA

"Almost always when chronic granulocytic leukemia is discovered, it has produced plenty of symptoms — fever, bone pain, anemia, a large spleen, etc. It's a rarity that you'll find this disease in an asymptomatic state. But if you do, it would be all right to watch it for a week or two, a month or two — to see what happens. Usually within two or three months, florid symptoms occur; and this disease is then ready to be tackled.

"The standard therapy today is busulfan (trade named Myleran). In recent years, we have used a number of agents—the antipurines and a number of mustard compounds, of which perhaps melphalan is the easiest for us to handle and has given us about as good results as any.

"Remissions, if the disease is correctly diagnosed, approach 100 percent. The disease is very nicely controlled by chemotherapy — possibly by radiation therapy, although in our opinion this is a little obsolete. . . . We maintain therapy year in and year out. Then at about three to four years, the striking limitation of present-day therapy shows up; namely, this disease becomes acute and fatally exacerbates. This is a disease that, in our experience, is geared up for about three, four or five years. Exacerbations occur then, either slowly or acutely; and it is a rarity that you can accomplish anything worthwhile from then on. Now this disease does not run long enough ordinarily for this reason to produce later complications that you will see in polycythemia vera and myeloid metaplasia. . . . In my knowledge of this disease, the problem is not to get agents that are more effective at the moment, but to find those that will keep the disease from going off the deep end in a matter of about three to four years."

—R. WAYNE RUNDLES, M.D., Durham, N.C.
Extracted from *Audio-Digest Internal Medicine,* Vol. 15, No. 23, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

MEDICAL STAFF CONFERENCE

The Clinical Pharmacology of Salicylates

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Associate Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. SMITH:* Our Medical Staff Conference may often seem like exercises in esoterica. Today we shall depart from that pattern. Every physician and, for that matter, every layman knows all about aspirin. It must be so, since this drug is used so widely and so casually. This morning we plan to review some of the facts which are known about this household drug with its remarkable versatility to produce beneficial and toxic effects. Despite the intensive study of pharmacologists, clinical pharmacologists, biochemists, and other investigators the residual questions outnumber the answers. Dr. Melmon will introduce this salicylate saga.

DR. MELMON:† Thank you, Dr. Smith. Dr. Rowland, Dr. Morrelli, and I would like to discuss a number of important aspects of salicylate therapy in man. I will begin the discussion with some historical background.

Historical Features

Aspirin is hardly new to clinical medicine with regard either to its use as a drug or to knowledge of its pharmacological activity. What is known of this activity had been described almost completely before the Christian era. Initially preparations of various barks were used for a variety of pharmacological effects such as treatment of sepsis, pain, fluid retention, gout, "corns," sciatica, and erysipelas. We will show that even today we know of few additional pharmacological properties or uses for aspirin. Even factitious "anemia" can be explained as the sole consequence of aspirin. For instance, it was well known by Greek surgeons that ingestion of small amounts of poplar bark or willow ash paste would exacerbate gout whereas very large amounts would prevent it. It is also interesting that the diuresis described by Aristotle when he first used madder bark occurred after the drug had been administered and discontinued, and not during the time the drug was being used. Therefore he felt that the drug preconditioned the individual for massive diuresis. Today we have confirmed Aristotle's finding, and I am sure he would be very happy to hear of our confidence in his work.

After Galen had used this drug, an era of disrepute followed, mainly because of St. Augustine's dictum that all diseases of Christians were to be ascribed to demons. Thus disease was a punishment, and physicians were reluctant to interfere with God's will, which resulted in the suppression of most available data on aspirin. Aspirin was rediscovered in a country kitchen by Edward Stone, who was traveling through the English countryside in search of a substitute for imported cinchona bark. He could not obtain the expensive Peruvian bark to treat his patients who had erysipelas and arthritis, and he was seeking a substitute. He actually wandered through the country on the faith of an old wives' tale told about the willow. I quote from some of his work: "As this tree delights in a moist or wet soil where aches chiefly abound, the general maxim that many natural maladies carry their cures along with them, or that their remedies lie not far from their causes, was so very apposite to this particular case that I could not help applying it. That this might be the intention of Providence had some little weight with me."[1,2]

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Then, having delivered himself of this rather shaky rationalization, Stone began his studies. He was able to gather 50 patients who were victims of agues and intermittent disorders. Although their seizures varied in severity, all were placed on the same regimen, reminiscent of modern studies. Each patient received 20 grams of powdered willow bark dissolved in a dram of water administered every four hours. The results, he was happy to record, "have been uniformly excellent."[2] Stone is one of the fathers of clinical pharmacology.

Thus we returned to the use of aspirin in some of its most native forms. In the nineteenth century people became interested in the compounds contained in these natural materials which made them so useful in clinical medicine. In Italy, Fontana and his coworkers began to isolate the active principles from willow bark. Later, in France, Larue found that he could isolate and purify the substance responsible for the therapeutic effect. In 1838 this substance was identified in Italy as salicylic acid. Finally in Germany, Kolb managed to synthesize salicylic acid, and today most salicylates have been synthesized.

Kolb found that salicylic acid alone was extremely efficacious but highly toxic, and several of its toxic manifestations were reported by him some time ago. While working in Germany he went to the Bayer Company to join a very good group of organic chemists interested in the interrelationships between organic and inorganic compounds. They very rapidly synthesized sodium salicylate and phenylsalicylate. However, the prize was left to Felix Hoffmann, a junior in the Bayer Company, whose father had severe rheumatoid arthritis. Hoffmann found that the new synthetics did help his father but that they were much too irritating to the gastric area for consistent ingestion. In his search for a better medication he rediscovered and synthesized yet another derivative, acetylsalicylic acid. He then made the conventional move. Having satisfied himself by laboratory tests and domestic trial of the worth of acetylsalicylic acid, he assembled his notes and carried them dutifully to the Bayer Company's director of pharmacological research, Heinrich Dreiser. Dreiser had been the architect of diacetylmorphine or heroin and was an imposing figure in European science.

Reacting to the data set before him in a manner befitting his rank, Dreiser took one look and took over. It was he who piloted acetylsalicylic acid through its first full clinical evaluation, and it was he who discarded the natural name as being hard to pronounce, hard to remember, and impossible to patent. He replaced it with the commercially seemlier name, aspirin. He cheerfully wrote and signed the pioneering report, confidently entitled "Aspirin," which first brought the compound to the attention of medicine. These events occurred toward the end of 1899; fortunately aspirin's merits took it from there.

Independently, the aboriginal tribes in Africa had found willow bark and leaves very effective in the treatment of rheumatism; however, our North American Indians were the most versatile in finding aspirin in a variety of substances largely forgotten for their salicylic acid content. They found it in the madder, the partridge berry, the grasses of wheat and rye, and in birch, beech jasmine, and poplar trees. They even found it in shrubs, peas, beans, and clover. The witch doctors had used all of these plants to great advantage.

Thus aspirin is one of the oldest compounds, senior to quinine, colchicine, and digitalis. It is also one of the least expensive and most widely used drugs in the world. At present the consumption of aspirin in the United States ranges between 27 and 74 million pounds a year. This massive consumption is alarming because aspirin is a dangerous drug. Between 17,000 and 100,000 cases of serious intoxication in children occur each year. Toxicity must not be taken lightly, for from 1 to 10 percent of these cases of intoxication result in death.

Pharmacological Effects of Salicylate Therapy

The administration of aspirin can lead to many problems. That aspirin may, in fact, increase the blood volume has long been known. One of its most characteristic effects is to promote retention of salt and water with a consequent weight gain. Aspirin has been administered in cases of acute rheumatic fever, yet investigators have stated that the drug does nothing for the myocardial lesion and the eventual complication of congestive failure. When aspirin is administered, fluid retention may bring about pulmonary edema at a time when the myocardium is not entirely competent.[3]

Several postulates have been made to explain this mechanism of fluid retention. Sodium retention and water retention which occur during administration of aspirin are predictable. In doses which produce analgesia a mild increase in fluid retention occurs even without excessive salt intake. Despite the fact that tools are available for the study of these phenomena, the mechanism of the sodium retention has not been examined. Volume changes are not due to release of anti-diuretic hormone (ADH), yet only a single study—published last year by Dr. Forsham's group—has attempted to investigate this point.[4] This *in vitro* study, using the toad bladder technique, found no effect of aspirin on ADH-like events. Although an increase in hydrocortisone excretion can occur, the effects of aspirin on osmotic changes, aldosterone secretion, and the anterior pituitary have not been explored. It is difficult to believe that a drug used this commonly and capable of producing these adverse effects has not been studied more thoroughly.

What we do know of the pharmacologic properties of aspirin is classical. For example, sophisticated studies have demonstrated that aspirin will increase oxygen consumption in man when administered in therapeutically useful doses. At 2×10^{-4} M concentration of aspirin, a concentration attainable in man, there is an uncoupling of oxidative phosphorylation in the mitochondria. This uncoupling is associated with a potassium leak and occurs after aspirin has attached to the mitochondrial membrane. The consequence of this uncoupling can be a decrease in tissue content of adenosine triphosphate (ATP) or a decrease in alternate types of high energy phosphate bonds. These effects are reversible when the drug is withdrawn or when the concentration in *in vitro* incubations has been reduced. Only at very high doses are dehydrogenase enzymes affected; the effect is an increase in oxygen consumption during the eumetabolic state. The clinical significance of these biochemical studies is not entirely defined, but it will not be surprising if the relationship between aspirin's biochemical properties and its pharmacological effects are found within the next few years.

Aspirin also affects carbohydrate metabolism. Although well known, this property has not been applied substantially to clinical medicine. After administration of aspirin, glucose levels rise in a normal person but fall in one who has diabetes. Aspirin does not prevent acidosis, but it does decrease the fasting blood sugar level and alters favorably the glucose tolerance test. The mechanism by which this occurs is not defined. It is not caused by an increased renal excretion of glucose (glycosuria is not the result of aspirin ingestion) nor by decreased gastrointestinal absorption of glucose. Hypervolemia cannot account for the total decrease in blood glucose concentration, nor is there evidence that aspirin can release insulin. Perhaps uncoupling of oxidative phosphorylation with a resultant increase in glucose uptake in peripheral tissues is the important pharmacological effect. Additional factors which may explain the hypoglycemic effects of aspirin include its ability to increase tissue glycolysis and to decrease glucose and glycogen synthesis from non-carbohydrate precursors. Whether aspirin could be used as an effective and safe oral hypoglycemic agent in a diabetic subject must be demonstrated by future investigation.

During acute intoxication aspirin produces hyperglycemia which occurs perhaps because of the direct effects of aspirin on both the adrenal medulla and the adrenal cortex. This action causes the adrenal medulla to release epinephrine, which in turn affects glucose metabolism. A second reaction may occur early in the administration of aspirin, leading to the depletion of hepatic glycogen stores. This depletion may be the result either of increased glycogenolysis, caused by catechol release from the adrenal, or of decreased glycogen synthesis.

A third effect of aspirin is its ability to decrease gastric motility and increase pylorospasm. This effect, related to the local concentration of the drug in the stomach, may result in sudden vomiting, although severe pylorospasm need not be associated with salicylism. Pylorospasm in adults can be severe, yet it is often unrecognized as an effect of aspirin. Despite delayed gastric emptying, aspirin can still be absorbed in the gut.

Still another pharmacological effect of aspirin is its influence on uric acid clearance. It is well known that low doses of aspirin affect distal tubular secretion of uric acid while high doses decrease proximal tubular reabsorption of uric acid. However, it is less well known that low concentrations of aspirin can result in xanthine oxidase inhibition. Whether this drug can be useful as an xanthine oxidase inhibitor has yet to be explored.

Although highly publicized, the endocrine effects of aspirin are not very important in clinical medicine. It is true that aspirin may release corticoids from the adrenal cortex, but extremely high doses are required. It is also true that because of its affinity for protein, aspirin can displace thyroid hormone and glucocorticoids from protein-binding sites. In addition, there is definite evidence that aspirin can decrease the production of thyroid stimulating hormone (TSH), but whether it affects other anterior pituitary hormones has not been studied. All of these pharmacological effects point to the need for additional research and indicate that aspirin is a potentially hazardous drug.

Aspirin is used mainly for its analgesic and anti-inflammatory properties. These two distinct types of pharmacological effects occur at distinctly different concentrations of the drug. Analgesia occurs at a much lower dosage level than is necessary for an anti-inflammatory effect. The major problem in the evaluation of these effects is the lack of adequate models for the study of analgesic and anti-inflammatory properties of drugs. What can we depend on? To begin with, the therapeutic index of this drug is remarkable. Secondly, pain produced by mechanical, electrical, thermal, or other noxious stimuli is not antagonized by salicylates or their congeners. Thirdly, we know that aspirin has no effect on the anticipation of pain. Finally, salicylates appear to work chemically in the area of the peripheral neuron. They antagonize a variety of substances which are thought to mediate pain at the tissue level — bradykinin, serotonin, histamine, and acetylcholine. All of these substances may mediate pain by their common ability to release potassium from neurons. At a very low concentration, potassium can stimulate pain receptor neurons and result in pain of a burning type. Similarly, in double-blind studies when the patient is unaware of the type of pain provocation used, aspirin antagonizes only this burning pain. Pain associated with tissue ischemia and acidosis likewise is antagonized by aspirin. Such pain is probably mediated by these same endogenous compounds.

Aspirin has its major clinical usefulness as an anti-inflammatory agent. However, little research has been carried out to compare the efficacy of salicylates with that of corticosteroids. There are obvious chemical and pharmacological differences in the anti-inflammatory effects of each agent. Clearly toxicity is less with aspirin than with anti-inflammatory doses of corticosteroids. Like steroids, aspirin produces anti-inflammatory effects in only the early phases of inflammation, that is, during periods associated with vasodilatation, increased capillary fragility, and edema formation. Aspirin and its congeners antagonize the types of inflammation which result in direct alteration of small vessels—for example, antibody interaction, thermal burns, bacterial invasion, or physical trauma. Salicylates could be effective because they interfere with mediators of the inflammatory reaction. However, there are no data that demonstrate direct chemical or antagonistic effects on histamine or that indicate an interaction of salicylates with serotonin or kinins. The effectiveness of salicylates may also be related to their ability to inhibit the production of mediators of inflammation. Indeed, this second theory is rapidly being confirmed by the accumulating evidence. There is evidence that aspirin may actually reach the neuronal receptor site and thus may prevent pain by interfering with the peripheral effects of the mediators. Finally, certain test situations have indicated that aspirin also may interfere with antigen-antibody reactions.

Salicylates do not have the same pharmacological effects as corticosteroids. To begin with, corticosteroids do not increase oxygen consumption or uncouple oxidative phosphorylation. Second, the altered protein metabolism produced by corticosteroids is not seen during administration of salicylates, nor is corticoid metabolism influenced by salicylates. Finally, salicylates have no ACTH-like effects unless taken in very high concentrations. There are no data describing the effects of salicylates on aldosterone secretion or on anterior pituitary function other than TSH production. What with our available investigational tools, it is difficult to believe that our knowledge is so inadequate.

The relationship between anti-inflammatory agents and the kinin system has been actively investigated.[5,6] Recent information on the anti-inflammatory effects of salicylate deals with kinin generation. Salicylates appear to prevent kinin generation by inhibiting the conversion of inactive kallikrein to its active form. Whether salicylates act by physically altering the enzyme precursor, the actual enzyme, or the enzyme substrate is not yet known. In some biological preparations salicylates block the effects of kinin. It has been demonstrated that endotoxin-antibody interaction in plasma can generate kinin leading to a subsequent depletion of kininogen. When aspirin in 5 x 10^{-5} M concentration is used in the *in vitro* incubation, there is remarkable inhibition of the kininogen depletion which would result in formation of kinin. The mechanism by which this occurs is not clear, but similar events have been recorded using both acetylsalicylic acid and sodium salicylate. Interestingly, corticosteroids do not work in such a preparation. Several investigators have demonstrated that kinin-induced pain, as well as pain produced by bronchial and smooth muscle constriction, is antagonized by therapeutic doses of aspirin.

In summary, research has shown that salicylates affect the kinin system in the following ways:

- Salicylates prevent kallikrein activation.
- Salicylates antagonize the peripheral effects of kinins, but they have no effect on kinin turnover.

There is a rationale for the use of salicylates. Most of the information has been gathered by pharmaceutical chemists rather than by clinicians. From their data it remains for us to extrapolate information valuable to clinical medicine. Dr. Malcolm Rowland will now discuss the salient points pertinent to the clinical use of salicylates. Some of the effects of salicylates have been summarized in Table 1.

TABLE 1.—*Pharmacological Effects of Salicylates*

1. Analgesia
2. Anti-inflammatory
3. Antipyrexia
4. Fluid retention
5. Increased oxygen consumption (uncoupling of oxidative phosphorylation)
6. Increased glucose tolerance (in diabetic)
7. Decreased gastric motility and increased pylorospasm
8. Diphasic effect on uric acid clearance
9. Endocrine:
    Decrease TSH
    Displace thyroxine and cortisol from binding proteins
    Stimulate adrenocortical hormone release (in high doses)

Pharmacokinetic and Biopharmaceutic Aspects

Dr. Rowland:* The pharmacokinetics of acetylsalicylic acid (ASA) and salicylic acid (SA) have been examined extensively. Studies have been undertaken to increase our understanding of the various processes (absorption, distribution, metabolism, and excretion) which determine the plasma or tissue concentrations of these agents following drug administration. Extrapolation of this information to clinical practice is based upon the reasonable assumption that some relationship exists between a pharmacological response and a given concentration of drug in plasma or tissue. Consequently, any factor which influences the pharmacokinetics of salicylates should similarly affect the pharmacological response-time curve. Since most salicylates are taken orally, any variable which can alter their absorption (for example, pharmaceutical dosage formulation) is important and will be considered. Whenever possible in this discussion, ASA and SA will be discussed separately since they differ chemically, pharmacologically and pharmacokinetically from each other. Since this discussion deals mainly with the clinical usage of salicylates, I refer the reader to a broader treatment of salicylates in the literature.[2,7,8]

ASA rather than SA has come into common usage because of the need for a chemical which is rapidly converted to SA upon entering the bloodstream but which does not produce the large amount of gastric irritation or have the extremely bitter taste associated with SA. Previous biopharmaceutical studies have made no attempt to distinguish between ASA and the metabolite SA, even though aspirin was usually the form administered. Only recently has information been obtained concerning the kinetics of absorption, distribution, excretion, and metabolism of ASA in man.

In their study of the effects of intravenous administration of ASA, Rowland and coworkers[9] found that the distribution phase, lasting approximately 20 minutes, was followed by an eliminination phase (Chart 1). The half-life (the time required for the plasma level of ASA to fall by 50 percent of its initial value) of the latter phase was 13 to 15 minutes. This rapid elimination time indicates that essentially no ASA is present in the body one hour after injection. Rapid elimination results almost entirely from the large amounts of esterases which hydrolyse ASA to SA. Following normal doses of aspirin these enzymes do not appear to be saturated. Urinary excretion of unchanged aspirin also occurs, but only 1 percent of the dose is lost by this route.[10] Because the conversion of ASA to SA occurs so rapidly and because the metabolism of SA is slower than that of ASA, SA levels rise sharply and persist long after all the ASA has been metabolized (Chart 1).

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Aspirin is usually given in solid dosage form, and dissolution of the drug must occur before absorption can take place. Therefore, in a recent study aspirin was administered in solution so that the intrinsic absorption of the drug could be determined.[11] When examined in this way, aspirin absorption was rapid, with peak levels occurring within 10 to 30 minutes. The half-life of the decline phase was also short, approximately 15 minutes, and only very low levels existed 2 hours following administration (Chart 2). In addition, the absorption process apparently followed first-order kinetics—that is, the rate of absorption was directly proportional to the amount of drug remaining in the gastrointestinal tract. In this study Rowland and coworkers[11] found that the inter-subject variation of the ASA absorption half-life was 3.5 to 16.0 minutes, even though the drug was given in solution (Chart 3). Possible reasons for this variation are suggested by the factors which control aspirin absorption. The drug must pass across the gastrointestinal tract to be absorbed, and it is generally assumed that only the un-ionized species is involved in the transport across this lipoidal-like membrane. The acidic environment of the stomach increases the percent of un-ionized aspirin (pKa 3.5), thereby favoring absorption. However, the greater surface area of the small intestine compensates for the more neutral pH, so that absorption of ASA occurs more rapidly in the small intestine than in the stomach. Hence, differences in stomach emptying time and, to a lesser extent, stomach pH are probably major reasons for variations in the absorption rate among subjects. Similar considerations should also hold for the absorption of SA (pKa 3.0).

Rowland and coworkers[12] also found that only 70 percent of the aspirin ingested reached the peripheral circulation intact. They based this conclusion on the finding that the area under the ASA plasma-time curve (a measure of the drug entering the peripheral circulation) was only 70 percent of that obtained with an equal intravenous dose. Subsequent analysis in animals revealed that esterases in the gut wall and high hepatic clearance of ASA were both responsible for this loss during absorption. While there is no direct evidence of their presence in man, esterases capable of hydrolysing ASA are known to exist in the intestinal tissue of the dog,[12] guinea pig[13] and rat.[14] Levy has shown that in the rat this enzyme system is capable of saturation at ASA concentrations ex-

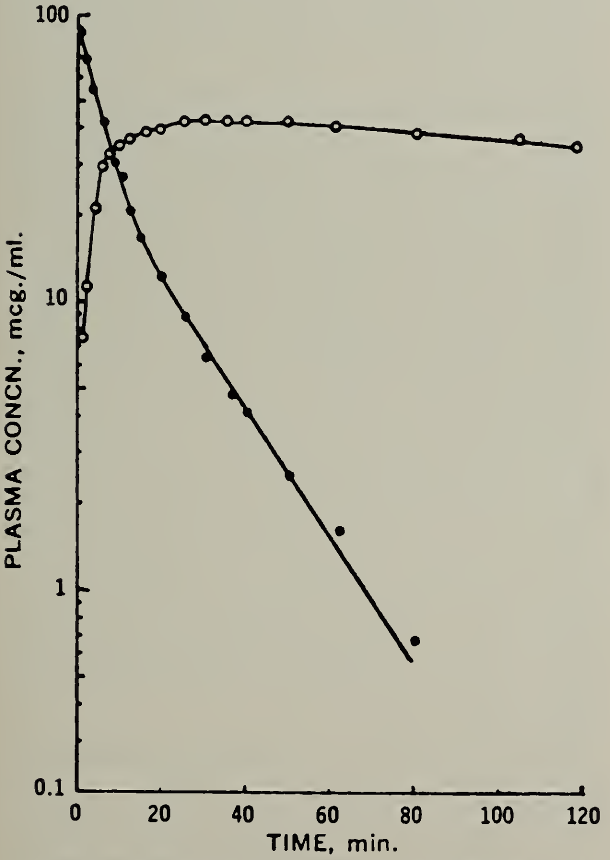

Chart 1.—Graph showing plasma concentrations of ASA and SA following intravenous administration of 650 mg ASA. Key: (●) ASA; (o) SA. (Reproduced with permission from J. Pharm. Sci., reference 9.)

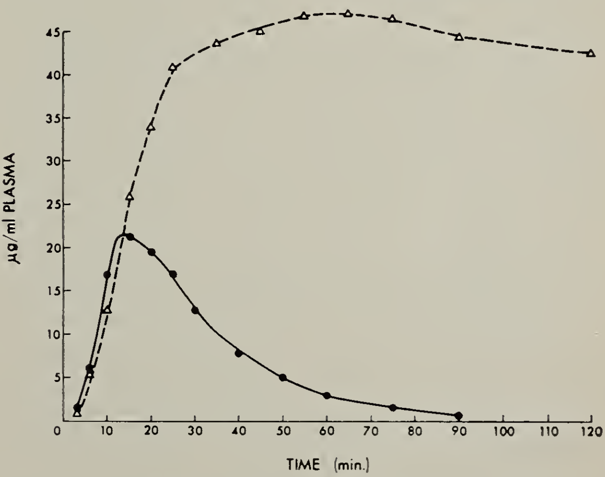

Chart 2.—Acetylsalicylic acid and salicylic acid plasma levels following administration in aqueous solution of 650 mg acetylsalicylic acid to a subject. Key: (●) Acetylsalicylic acid; (△) Salicylic acid.

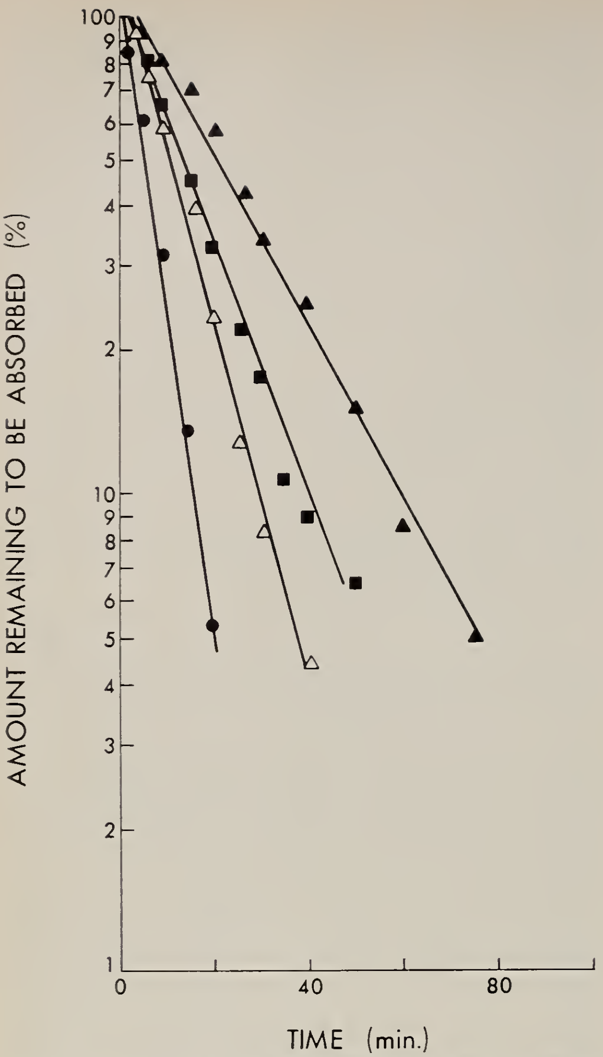

Chart 3.—Graph showing the amount of aspirin remaining to be absorbed following the ingestion of a solution of 650 mg of aspirin. The different symbols indicate the data from individual subjects.

pected in intestinal fluid. Rowland and coworkers[11] have observed that, in rabbits, esterase activity varies along the gastrointestinal tract, being maximal in the small intestine and minimal in the stomach. Although these findings cannot be applied directly to man, non-specific esterases have been found along the entire human gastrointestinal tract.[15] Consequently, the proportion of ingested ASA reaching the tissues is influenced by the dosage form administered. Those preparations which release the drug slowly into solution could result in ASA absorption at low concentrations in areas of the gastrointestinal tract where esterase activity is high. In addition, saturation of the enzyme may not occur, resulting in a greater loss of drug during absorption with this formulation than with a rapidly dissolving dosage form.

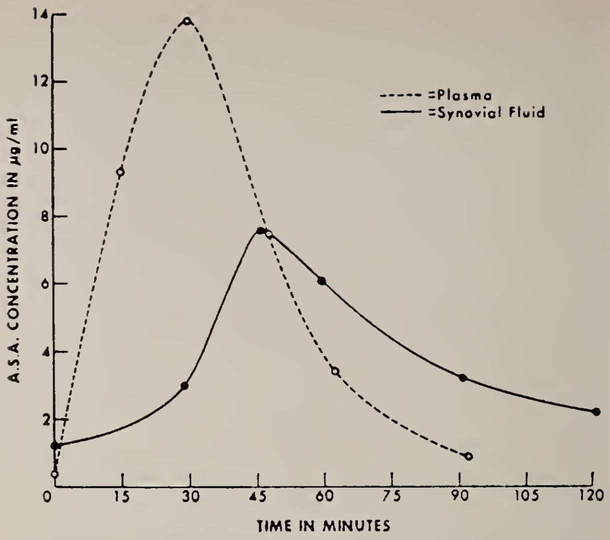

Chart 4.—Drug concentrations in plasma and synovial fluid from one patient after ingestion of 20 gr of acetylsalicylic acid. Zero time is 2½ hours after the patient had inadvertently taken 10 gr of aspirin. (Reproduced with permission from Arthritis and Rheumat., reference 16.)

Clinically these findings become relevant only when it is necessary to achieve significant ASA rather than SA levels. This is the goal when aspirin is used as an analgesic, since ASA is more potent than its metabolite SA. In this case a rapidly absorbed dosage form is important not only because it allows more intact drug to reach the tissues but because it is absorbed more rapidly, resulting in earlier and greater peak plasma levels and earlier pharmacological effects. As the half-life for absorption becomes longer, the time required to reach maximum plasma content increases and the magnitude of the content decreases. If absorption is too slow, an effective level of aspirin may not be reached. On the other hand, because the half-life of SA is much longer than that of ASA, normal variations in the absorption rate of aspirin do not appreciably influence the resultant content of SA. Although most of the above discussion has been related to plasma levels of salicylates, these drugs act at some site in tissue. If distribution into tissue is slow, as occurs in synovial fluid (Chart 4),[16] peak tissue levels and, consequently, maximum pharmacological effects will be subsequent to peak plasma levels.

Numerous studies have demonstrated large differences in the absorption rate of aspirin from various dosage forms. The most rapid absorption is achieved when aspirin is given in solution as an effervescent mixture. However, these mixtures have two major disadvantages. They are highly

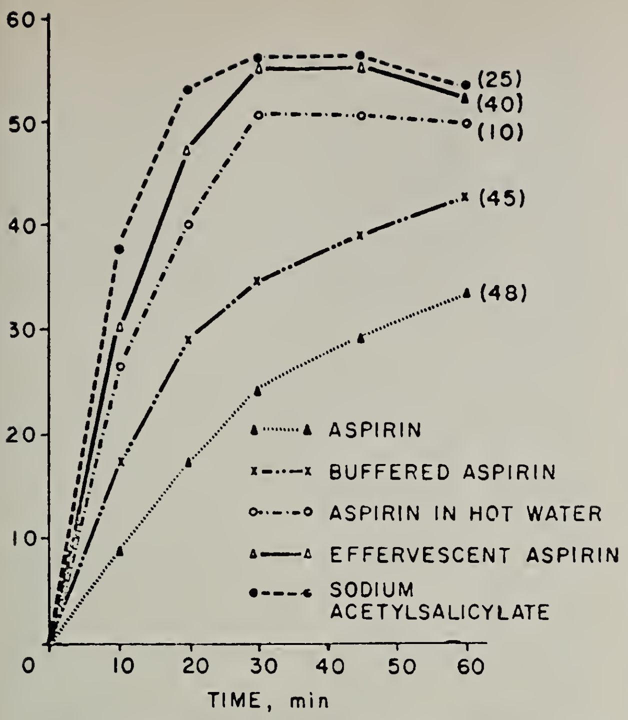

Chart 5.—Plasma total salicylate concentrations following the oral ingestion of various preparations of aspirin. The total dose was equivalent to 640 mg of aspirin in all cases. Figures in parentheses represent the number of human subjects studied in each group. (Reproduced with permission from Clin. Pharmacol. Ther., reference 17.)

alkaline and may produce alkalosis if ingested often; and because of their high sodium content, they cannot be given to persons with restricted sodium intake. In general, buffered aspirin tablets are more rapidly absorbed than are plain aspirin tablets (Chart 5).[17] The buffered tablets are formulated with basic ingredients which tend to produce a higher pH in the immediate vicinity of the aspirin particles than in the surrounding gastric medium. Since sodium aspirin is much more soluble than the free acid, a higher concentration of aspirin exists around the dissolving aspirin particles in the buffered preparations than around aspirin formulated alone. As the rate of dissolution and, hence, absorption is dependent on the concentration difference of drug between that at the surface of the dissolving aspirin tablet and that in the intestinal fluids, absorption should be faster from buffered aspirin preparations. Further studies have suggested that other variables in tablet formulation may be important.[18,19] Changes in motility, viscosity and pH of the gastrointestinal contents may also influence dissolution and, therefore, the absorption of the drug.

To avoid the problem of gastric disturbances observed in some patients receiving salicylate therapy, both aspirin and sodium salicylate are occasionally administered as enteric coated tablets. In these tablets the drug is coated with a material resistant to acid but not to intestinal fluids, thereby preventing drug release in the stomach. Although satisfactory in theory, generally these products have not proved as reliable as uncoated tablets, either because breakdown occurs in the stomach or absorption is incomplete.[20,21] Enteric coated tablets vary more widely in rate of absorption after ingestion than do the uncoated forms[22] and they are characterized by a lag period as long as 20 hours before absorption takes place (Chart 6). Accordingly, enteric coated salicylate tablets should not be given when an immediate effect is desired—that is, when used as an anti-pyretic or analgesic agent. In these circumstances it has been recommended that aspirin be taken in solution or as a reliable uncoated tablet with plenty of water.

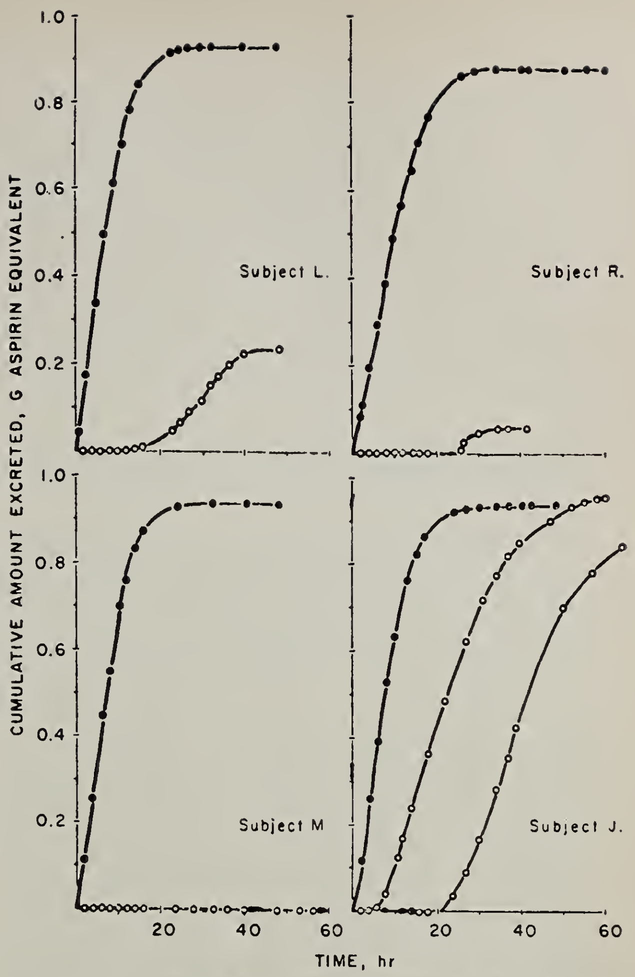

Chart 6.—Cumulative urinary excretion of salicylate, expressed in terms of aspirin, as a function of time after ingestion of 1 gr aspirin. Key: (●) in solution; (o) in enteric coated tablets. (Reproduced with permission from N.Y. State J. Med., reference 20.)

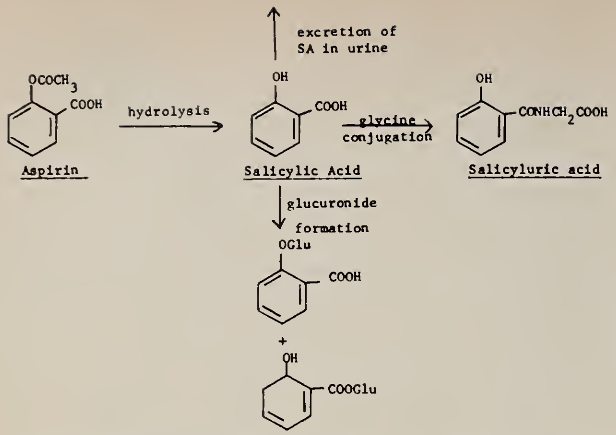

Chart 7.—Scheme depicting the formation and elimination of salicylic acid from the body.

Most patients suffering from rheumatoid arthritis still rely on salicylate therapy for relief of symptoms even though other drugs are available. Although they do not constitute the majority of persons taking aspirin, these patients may consume the greatest quantity, frequently ingesting 2 to 6 grams daily for extensive periods. At present ASA and SA appear to be equivalent as anti-inflammatory agents. Therefore aspirin can be considered purely as a convenient source for the delivery of SA to the body, since aspirin is almost completely hydrolyzed before significant loss of SA takes place. A unique feature of SA kinetics which occurs in the therapeutic dosage range, but which is not seen following ASA administration, is the increase in the apparent half-life of SA with increasing dosage. Thus, following a single tablet (0.3 grams) the half-life of SA is approximately 2.5 hours. At a dose of 1.0 gram it is approximately 7 hours, while a half-life of 19 hours has been reported after administration of 10 to 20 grams of SA.[23] This phenomenon is shown in Chart 7 which depicts the elimination of SA from the body. After absorption of SA the drug is eliminated as its glycine conjugate (salicyluric acid), phenolic and ester glucuronides, or it is excreted unchanged in the urine. When the dose is 0.3 grams or less, the percentages of these materials found in the urine are 80, 10 to 20, and 2 to 5, respectively. However, when the amount of SA in the body is greater than 0.3 grams, the capacity to form salicyluric acid is exceeded; that is, the rate of formation of salicyluric acid becomes maximal and constant. Consequently, while the rate of salicyluric acid excretion remains essentialy the same with increasing dose, the fractional rate of drug loss from the body decreases, the half-life for elimination increases, and a greater proportion is excreted as unchanged drug. Finally, at very high doses (10-20 grams) elimination occurs almost exclusively by urinary excretion of SA and the half-life approaches 20 hours, a value frequently observed in patients being treated for rheumatoid arthritis and in salicylate intoxication.[23] Above 0.3 grams the contribution of salicyluric acid formation to overall elimination changes continuously, as does the apparent half-life of SA.

From the foregoing discussion it is clear that patients with rheumatoid arthritis who ingest large doses of salicylate over long periods achieve a self-sustaining level of SA in blood and tissues. For this reason, prolonged release dosage forms of this drug are probably not warranted in this group of patients. SA is only one example of dose-dependent kinetics. Others include dicoumarol and phenylbutazone.[24,25] Therefore, for drugs which exhibit this phenomenon in the therapeutic dosage range, more attention will be required in the establishment of suitable dosage regimens.

The measured excretion of unchanged SA is the net effect of glomerular filtration of plasma water, active secretion of drug into the proximal convoluted tubular fluid, and passive reabsorption in the distal convoluted tubules. When passive reabsorption exceeds the first two processes, no SA is found in the urine. Important factors influencing reabsorption are urinary pH and flow rate. The driving force for reabsorption is the difference between the concentration of un-ionized drug in the luminar fluid and that in the peritubular blood vessels. As urinary pH increases from 5 to 8 the fraction and, therefore, the concentration of un-ionized acid decreases. This rise in pH, therefore, diminishes reabsorption and increases net urinary excretion of salicylate. In fact, McPherson and coworkers have shown that with a urine pH below 6.0, SA is almost completely reabsorbed, while a change of only one pH unit, from 7 to 8, raises the excretion rate five-fold.[26] Diuresis increases excretion of salicylate by diluting all urinary constituents, which leads to a subsequent decrease in reabsorption. Clinically the excretion of SA becomes important only when this is a significant route of elimination of salicylate from the body. As mentioned, this occurs only at high dosage levels and, when these arise from intoxication, alkaline diuresis has proved an effective means of hastening salicylate elimination.[27]

Like many other acidic drugs ASA and SA are bound to plasma proteins, particularly albumin. Since both drugs are ionized over 99 percent at physiological pH, it is probable that the ionized form rather than the un-ionized one is involved in the interaction. Consequently, normal changes in plasma pH have little effect on this protein binding. Salicylate is bound more extensively than acetylsalicylate, so that at the same plasma concentration less SA is available in plasma water to diffuse and interact at its site of action. The actual proportion of protein binding varies with the concentration of both drug and plasma protein. Increasing the concentration of salicylate leads to a decrease in the proportion that is bound. Similarly a decrease in albumin results in more unbound salicylate, which then diffuses from the blood into tissues and thereby lowers the total (bound and unbound) plasma salicylate levels.[28] This sequence of events occurs in states associated with hypoalbuminemia.[29] Because of an increase in the concentration of diffusable drug, salicylate may be more effective in these situations.

A knowledge of the pharmacokinetics and biopharmaceutics of ASA and SA is necessary if these drugs are to be used wisely. This information not only leads to a better understanding of the appropriate dosage regimen for each agent but stresses the importance of the dosage form. It also indicates the direction of treatment in cases of salicylate toxicity. Although extensive studies of these drugs have been conducted, they have only partially focused on the problem of salicylates in drug interactions. The relevance of this latter consideration to clinical medicine remains to be ascertained.

Clinical Problems Associated with Salicylate Therapy

DR. MORRELLI:* Because of lack of time we have decided to omit a formal case presentation of the next patient, but I would like to summarize the critical features of the case. A young woman entered the hospital after ingestion of a large amount of aspirin. The important features during the first three days in hospital were profound alkalosis with a blood pH of 7.6 and a blood pCO_2 level as low as 10 mm of mercury. During this period the urine was persistently acid. In addition, serum salicylate levels fell slowly and severe hypokalemia developed and continued despite vigorous attempts at replacement therapy.

I would like to discuss salicylate ingestion from two general themes: (1) Treatment of serious symptoms that result immediately following aspirin ingestion and (2) Methods for increasing the excretion of salicylates. Many of the major clinical problems have been discussed already. Hyperthermia is a problem in infancy. The problem of renal damage from chronic or acute aspirin ingestion is unresolved, but renal cells have been found in the urine of patients who take large amounts of salicylates, and occasionally tubular necrosis has been reported after aspirin ingestion. It is difficult to determine whether such renal damage is due directly to the aspirin or secondarily to dehydration, hypovolemia, and hypotension. Hemorrhage does occur and can be gross or petechial as a result of hypoprothrombinemia, thrombocytopenia or a direct effect of aspirin on small blood vessels.

The problem of acid-base balance and electrolyte losses following aspirin ingestion requires some emphasis. There is a major difference between adults and children with regard to the type of electrolyte abnormality seen in aspirin poisoning. In adults the initial effect is an increase in alveolar ventilation, leading to respiratory alkalosis. Although renal compensatory mechanisms are called into play, they are fairly slow, and alkalosis persists for some time. The effect of aspirin on metabolic rate may lead to increased carbon dioxide generation, but this increase is not enough in most cases to compensate for the alkalosis. Similarly, many patients with aspirin poisoning vomit, contributing to systemic alkalosis. A paradoxical aciduria—that is, acid urine despite systemic alkalosis, may be due in large part to sodium and potassium depletion and respiratory alkalosis, both of which affect the ability of the kidneys to excrete hydrogen ion.

In children a different physiological pattern is seen. Although there may be a slight increase in alveolar ventilation, this is readily overcome by the metabolic effects of aspirin in infants and in children below 5 years of age. In these patients a striking increase in basal metabolic rate and carbon dioxide production as well as the appearance in the circulation of so-called unmeasured anions such as pyruvate, malate, fumarate and acetoacetate account for the profound acidosis. The kidney is not able to keep pace with this large acid load, and the loss of acid through vomiting is insufficient to compensate for these metabolic derangements. Such young patients, therefore, usually have a profound metabolic acidosis after excessive aspirin ingestion.

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Other fluid and electrolyte abnormalities in aspirin poisoning include dehydration as a result of vomiting and sweating, and sodium depletion as a result of vomiting and renal losses, as well as occasional massive sodium loss by sweating. These problems, in conjunction with respiratory alkalosis in adults, may lead to very profound degrees of potassium depletion. The importance of potassium depletion in aspirin poisoning was recognized as early as 1959. In 1964 Beveridge and coworkers[30] reported upon 18 patients with serum salicylate levels greater than 50 mg per 100 ml who had serum potassium levels that were almost uniformly in the hypokalemic range. Accordingly, then, patients with serious aspirin intoxication need water, sodium, potassium, and possibly bicarbonate for alkalinization of the urine. It is criticial to alkalinize the urine if fluid therapy is to be the sole manner in which salicylates are removed from the body.

Many methods are available for increasing the removal of salicylates. Gastric lavage should be done in all patients with known salicylate poisoning, since gastric emptying may be quite delayed. If the patient is comatose, an endotracheal tube is necessary to prevent aspiration of stomach contents. Osmotic diuresis has been effective in the removal of salicylates, but when agents such as mannitol are used, diuresis is attended by other problems such as primary renal damage. In pediatric wards exchange transfusion is a widely used method for management of aspirin intoxication because pediatricians are quite familiar with the techniques of this procedure. Although peritoneal dialysis is effective and could be utilized in either pediatric or adult medicine, hemodialysis is the quickest method for removal of salicylates, given easy access to the dialysis procedure. Alkalinization of the urine can be accomplished in many ways. Patients do it themselves early in aspirin poisoning by hyperventilation, but as sodium and potassium depletion ensues, the urine becomes acid due to insufficient cations. Sodium bicarbonate therapy has been used for alkalinization even in the presence of a blood pH of 7.5 or 7.6. This approach has been used effectively by British investigators.[31] Finally, such drugs as acetazolamide which prevent bicarbonate reabsorption produce alkaline urine and greatly enhance salicylate clearance.

With regard to the dialysis methods for removing salicylates, the study by Done[32] indicates that hemodialysis is much quicker than other procedures. This study was done in dogs that had been given an acute toxic dose of salicylates. In this setting it is easier to prove the effectiveness of hemodialysis than it is in clinical situations where hemodialysis is not readily available. An attempt to facilitate the clearance of salicylate was made by adding albumin to the dialysate. Although this does accelerate to a limited extent the removal of salicylate from the body, it could be an extraordinarily high price to pay for the limited difference in clearance rate of salicylates.

How, then, should the decision be made as to the use of alkaline diuresis, peritoneal dialysis, or hemodialysis? Done[32] has classified the severity of salicylate poisoning by symptomatology:

- No Symptoms: occasional subjective but no objective manifestations.
- Mild Intoxication: mild to moderate hyperpnea, sometimes lethargy.
- Moderate Intoxication: severe hyperpnea, prominent neurological disturbances, pronounced lethargy and/or excitability, but not coma or convulsions.
- Severe Intoxication: severe hyperpnea, coma or semi-coma with or without convulsions, and cardiovascular collapse.

An attempt to correlate the severity of symptoms with the actual blood level of salicylate led to some difficulties. Because little correlation could be established with blood levels reported at the time of admission to the hospital, an attempt was made to estimate the blood salicylate level shortly after ingestion of the salicylate by using an estimated half-life of 20 hours for the drug. Using this calculation, a dose correlation could be established between the estimated blood level shortly after ingestion and the severity of symptoms. The use of such a method together with the availability of hemodialysis methods should aid in decision as to the most appropriate method of therapy for salicylate intoxication.

A number of other clinical problems occur as side-effects of aspirin therapy. In addition to the types of intoxication which have been discussed, allergic response to aspirin is not uncommon. This includes skin rashes, urticaria, edema and asthma, with rare anaphylactic reactions. The mechanism of these types of hypersensitivity are poorly understood; for example, aspirin causes asthma more frequently than it causes skin rashes. Para-amino salicylic acid, on the other hand, which is close structurally to aspirin, causes skin rashes but almost never causes asthma.

Gastrointestinal bleeding is a common problem following aspirin ingestion. Minor degrees of gastrointestinal bleeding (loss of less than 5 ml of blood per day as determined by chromium-tagged red blood cell studies) occurs in probably 70 percent of patients who take aspirin in a dose range of 3 to 6 grams per day. Larger amounts of blood loss, 10 to 100 ml per day, sometimes occur but the incidence of this degree of bleeding is not known. Severe gastrointestinal hemorrhage after aspirin intake has been reported, but again the true incidence is not established. This topic was reviewed recently.[33]

Similarly, the mechanisms by which aspirin induces gastrointestinal bleeding are the subject of considerable debate and guesswork. Some investigators feel that aspirin has a direct local irritant effect with or without such systemic effects as histamine release or alteration in prothrombin time. Some investigators feel more strongly that it is related to a systemic response involving blood vessels directly, complicated by changes in clotting factors. Again no definite conclusion can be made.

The emphasis placed on gastrointestinal bleeding as a complication of aspirin therapy has led to the development of a number of special aspirin formulations. These include effervescent solutions, buffered aspirin, enteric-coated tablets, glycine aspirin, and calcium aspirin plus urea. There are a number of studies on this subject, some confirming and some denying the ability of these compounds to reduce the incidence of gastrointestinal bleeding. It is true that effervescent solutions of aspirin do cause less gastrointestinal bleeding than regular aspirin. However, the amount of bicarbonate accompanying 3 to 6 grams of aspirin per day may lead to severe alkalosis. Dr. Rowland has pointed out that enteric coated tablets are not absorbed well by many patients, which probably accounts for the few studies which indicate that enteric coating will prevent gastrointestinal bleeding.

There are a few toxic symptoms (such as tinnitus, deafness, nausea, vomiting, hyperventilation, and dyspnea) which may require some change in dosage. These are common and are not particularly serious. The serious complications of aspirin intoxication—hemorrhage, pulmonary edema, incapacitating vertigo, drowsiness and, very rarely, mental dysfunction—are rare. Some of the toxic effects of salicylates have been summarized in (Table 2).

TABLE 2.—*Symptoms of Toxicity of Salicylates*

Hyperventilation with respiratory alkalosis (adults)
Metabolic acidosis (children)
Hypokalemia
Allergic reactions — skin rashes, urticaria, edema, asthma, rarely anaphylactic reactions
Gastrointestinal bleeding
Central nervous system—tinnitus, deafness, vertigo, drowsiness, rarely mental dysfunction
Hyperthermia (infants)
Depression of prothrombin, platelet dysfunction, possibly increased fragility of small blood vessels
Possibly direct renal damage — Aspirin may have a role in analgesic nephritis.

Dr. Smith: We have heard a very impressive example of how new sophistication can be brought to the study of a very common drug. A question that comes to mind from these discussions is: Why is salicylic acid found in so many plants? This suggests that it may be a normal metabolite in plants and perhaps has some function. Is its metabolism in plants known, and is salicylic acid a normal metabolite in human or mammalian systems if searched for by sensitive analytical techniques?

Dr. Rowland: I do not know why so many plants have salicylic acid in them. It may be a useless metabolic end-product such as oxalic acid. In humans there is no evidence that salicylic acid is present in normal tissues.

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SALICYLATES IN RHEUMATOID ARTHRITIS

"The drug of choice — the drug that is recommended almost universally for rheumatoid arthritis — is the salicylate. The salicylates are part of the so-called basic or conservative management program, which also includes physicial therapy, rest, and orthopedic appliances. . . . But it's only in very recent years that physicians have demonstrated quite satisfactorily that salicylates also have an anti-inflammatory effect in rheumatoid arthritis.

"The rub here, of course, is that excess doses — or what may be *called* excess doses — are needed in order to exert the anti-inflammatory effect. The peak blood level of salicylate occurs about two and a half hours following ingestion; so that theoretically at least, it would be desirable to give patients salicylates every four hours around the clock in order to provide the optimal anti-inflammatory effect. Plasma levels of 10 to 20 mg per 100 ml are said to be the ideal level for the anti-inflammatory effect; perhaps we should be doing them more frequently. But one can use tinnitus as a guide to dose. Generally speaking, the appearance of tinnitus indicates an optimal level; and one should drop down ever so slightly below the level of tinnitus."

—Ephraim P. Engleman, M.D., San Francisco
Extracted from *Audio-Digest Internal Medicine,* Vol. 15, No. 24, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

Government and Medicine

Physicians as Employers

HOWARD HASSARD, *San Francisco*

MANY PHYSICIANS APPARENTLY do not know that when they employ other persons to assist them in their practice of medicine they become subject to certain responsibilities to the employees and to the state and federal governments. Yet neglect of any of these obligations may be costly to them in money or cause them to face time-consuming interviews by government investigators.

This article will deal with some of the obligations the physician incurs as an employer under the Federal Income and Employer's Taxes, Unemployment Compensation Insurance (State and Federal) and California Workmen's Compensation and other related labor laws.

Federal Withholding Tax Requirements

The Internal Revenue Code requires that all employers withhold specified portions from whatever wages are paid. "Wages" include, besides cash, the cash value of any remuneration paid in a medium other than cash. There are exceptions to this rule, but they would generally not arise in the practice of medicine.

The amount to be withheld from each employee is to be determined in accordance with tables published by the Internal Revenue Service. Entry to the tables is by reference to wages paid the employee and the number of lawful exemptions he claims. Under the Internal Revenue Code, the employer is required to hold withheld tax monies in trust for the Federal Government. These funds must be turned over to the Internal Revenue Service periodically — quarterly, monthly or semimonthly, depending upon the total amount withheld by the employer. If the total amount withheld from all employees is less than $100 a month, the funds withheld must be delivered to the Internal Revenue Service quarterly; if more than $100 but less than $2,500 a month, the funds must be transmitted monthly; if more than $2,500 a month, semi-monthly. The Internal Revenue Service provides the various forms which must be completed when transmitting the funds.

An employer is also responsible for the preparation and distribution of W-2 forms and for acquiring and maintaining W-4 and W-3 forms. The W-2 forms are annual statements to be prepared by an employer before 31 January of each year for each employee, showing the amounts withheld from the employee. The W-3 form, which shows the total amount withheld from all employees by the employer, also must be prepared before 31 January. The W-4 form shows the number of exemptions an employee claims he is entitled to under the law. It is prepared by the employee, and the employer is not responsible for verifying the validity of the information given by the employee. He is responsible, however, for seeing that each employee does complete and file such a form with the employer, and he must keep the completed form on file.

The author is legal counsel for the California Medical Association.

Submitted 27 February 1969.

Reprint requests to: 693 Sutter Street, San Francisco 94102.

Federal Employment Taxes

In addition to withholding the previously mentioned sums for income tax purposes, an employer must also withhold specified amounts for Federal Employment Taxes. There are two basic Federal Employment Taxes. They are the Federal Insurance Contribution Act (FICA) and the Federal Unemployment Tax Act (FUTA).

Federal Insurance Contribution Act (Social Security)

Under the Federal Insurance Contribution Act (often referred to as Social Security), as it stood at the beginning of 1969, an employer must withhold 4.9 percent of the wages of an employee that do not exceed $6,600 a year. In addition the FICA imposes a tax on the employer equal to the amount withheld from the employee under the FICA law. The FICA withholdings from employees' wages are to be taken into account by the employer in determining how often he must remit to the Internal Revenue Service.

Federal Unemployment Tax Act

Besides FICA contributions, an employer may also be liable for a Federal Unemployment Tax. Employers who employ four or more persons for a period of 20 days or more in one year are subject to the Federal Unemployment Tax Act (FUTA) which at present levies a rate of 3.1 percent of the first $3,000 per year of each employee's wages. (A credit may be applied and is allowed against the employer's FUTA tax for amounts paid by an employer to a qualified State Unemployment Insurance Fund. California has a qualified State Unemployment Insurance Fund.)

The tax rates under both FICA and FUTA are constantly being changed. Hence, in computing the taxes, the employer should always make sure that he is using the up-to-date rate.

Penalties

Violation of any of these laws can result in serious penalties. The extent of the penalties depends upon whether or not the non-compliance was wilful or fraudulent. Wilful or fraudulent noncompliance can be a criminal offense, with the possibility of a fine and sentence being imposed.

Usually an employer who neglects to withhold taxes from an employee is held personally liable for the amounts not withheld. Interest up to 6 percent is charged on withheld funds that are not deposited on time.

Failure of the employer to pay the taxes imposed upon himself, as an employer, can result in a penalty assessment equal to 50 percent of the tax where there was intent to defraud or evade taxes. If there was no such intent, the penalty assessment would be 5 percent of the taxes not paid.

Failure to file informational returns can also result in penalties. The penalty is usually $10 per form not filed, up to a maximum of $25,000.

A physician who wants to know what all this means to him should apply the rules to his own circumstances. Say, for example, he employs a registered nurse at $500 a month and a medical assistant at $300 a month, and that he fails to withhold FICA and income taxes, and does not file the W-2 and W-3 forms and also neglects to pay the FICA tax imposed on himself as an employer: At the end of only one year he would have incurred a tax liability of more than $2,300 over and above what he otherwise would have been required to pay.

California Unemployment Insurance

California has enacted a Federally-qualified Unemployment Insurance Program. Under it, each employer,* is required to contribute a specified amount to the fund. The amount is determined by the total wages paid by the employer, the charges that have been made against the fund during the preceding 36-month period to pay unemployment benefits to persons discharged from his employ, and the status of the Unemployment Insurance Fund. At present the maximum amount an employer may be liable for is 3.7 percent of $3,800 per employee. The actual contribution required is determined by a complicated scale which ranges downward from the 3.7 percent maximum, depending on the employer's experience and the Fund's total reserves.

The California Unemployment Act places a tax on the employee too—1 percent of the first $7,400 of wages received in a year. The employer is responsible for withholding this amount. A further provision is that a self-employed person (i.e. the physician) may elect to pay a tax of 1.5 percent on the first $7,400 of his own earnings, and thereby afford himself unemployment insurance coverage.

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*The Act defines an employer as anyone who employs one or more persons for more than one day and pays a total of wages exceeding $100 per quarter.

The employer's payments on his own account and the remittances of the taxes withheld from employees' pay are due quarterly but the payment dates are different for the former than for the latter. For his own account, the due dates are in March, June, September and December; for employees, February, May, August and November. Penalties up to 25 percent of the amount due can be imposed for failure to comply with the Act.

Workmen's Compensation

California has a law, commonly referred to as the Workmen's Compensation Act, which provides that when an employee is covered by the Act and his employer is subject to it,* the employee's sole claim against his employer for injury in the course of his job shall be the compensation provided for by the Act.

To recover compensation under the Act, an employee need only show (1) that he and his employer are subject to the Act; (2) that he was injured in the course of his employment; (3) that the cause of injury was related to the employment; and (4) that injury was not self-inflicted or caused by his own wilful intoxication or incurred in a melee in which he was an aggressor. The employee does not need to show negligence on the part of his employer or anyone else in order to recover compensation. Furthermore, an employer cannot defeat recovery under the Workmen's Compensation Act by showing that the employee, himself, was negligent or had assumed the risk or the injury involved. In other words, when the Act is applicable an employee will be compensated for all injuries caused by and arising out of the employment without regard to fault.

In turn, the employee can recover from his employer only that compensation available and allowed under the Act. However, the Act does not bar the employee from suing a third person (other than his employer) for his injuries.

The California Workmen's Compensation Act requires every employer to carry Workmen's Compensation insurance, unless the employer obtains a certificate of consent to self-insure from the Director of Industrial Relations. An employer who does not comply with the Act forfeits the protections afforded the employer by the Act. The employee then may bring actions beyond the limits set in the Act. In addition negligence on the employer's part will be *presumed* and the only affirmative defenses allowed the employer are those of self-infliction of injury or that injury was caused by wilful intoxication or being the aggressor in a melee.

IMPORTANT FILING DATES

Semi-monthly

- **Payment of employee net wages after withholding.**
- **Transmittal to IRS of withheld employee income and Social Security taxes, together with employers' contribution, if total exceeds $2,500.**

Monthly

- **Transmittal to IRS of withheld employee income and Social Security taxes, together with employers' contribution, if total exceeds $100.**

Quarterly

- **Transmittal to IRS of balance of withheld employee income and Social Security taxes and employer Social Security contribution.**
- **Payment of California Unemployment Act employee taxes (February, May, August and November) and taxes of employer electing to be included (March, June, September and December).**

California Labor Laws and Fair Employment Practices Act

Two other California laws apply to physicians as employers: (1) California Labor Code provisions relating to time for payment of wages, and (2) The California Fair Employment Practices Act.

Payment of Wages

The California Labor Code provides that an employer must pay his employees for wages earned at least twice during each calendar month. When the labor or services were performed by the employee between the 1st and 15th, the employee must be paid between the 16th and 26th of each month. When work is performed between the 16th and the last day of the month, payment must be made between the 1st and 10th of the following month. In addition, an employer must post in a conspicuous place a notice indicating the regular pay days. Whenever he is paid, the employee must be given an itemized account showing all deductions, the period the employee is being paid for, the Social Security number and name of the employee.

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*For all practical purposes, all California employers and employees are subject to the provisions and terms of the California Workmen's Compensation Act.

In the event an employee is discharged, he must be paid all his earned wages within 72 hours. If an employee voluntarily quits his employment, his wages are also due within 72 hours, except that if he has given 72 hours' notice of termination, his wages are due at the time his employment ends.

Minimum Wages and Maintenance of Records

California has enacted laws establishing minimum wages for women and minors. There are also laws establishing maximum hours of work by women and minors. At present, the minimum wage for females who would be employed in various capacities in physicians' offices is $1.65 per hour. Female employees are limited to an eight-hour workday, and a maximum workweek of 48 hours. The eight hour limit may be exceeded in an "emergency," which means "an unpredictable or unavoidable occurrence at unscheduled intervals requiring immediate action."

California law requires that each employer must maintain records which include the following information:

(1) Full name, home address, occupation and Social Security number.

(2) Birth date, if under eighteen years, and designation as a minor.

(3) Time records showing all in-and-out time which shall be recorded when the employee begins and ends each work period. Meal periods, split shift intervals and total daily hours worked shall also be recorded. Meal periods during which operations cease and authorized rest periods need not be recorded.

(4) Total wages paid each payroll period.

(5) Total hours worked in the payroll period.

Discharged or disgruntled employees occasionally complain to the State Labor Commissioner that required overtime payments have not been made. In general, overtime hours must be compensated for at no less than one and one-half the regular rate of pay. If adequate time records have not been maintained, it may be difficult to refute such claims.

California Fair Employment Practices Act

The California Fair Employment Practices Act prohibits employers from indulging in any employment practices which discriminate against a person because of his race, religious creed, color, national origin or ancestry.

The California Fair Employment Practice Commission is authorized to investigate all complaints of discriminatory employment practices and to seek court injunction of the practices if it finds the complaints valid. Any person who wilfully violates any order of the Commission may be charged with a misdemeanor.

Civil Rights Act

In addition to the Fair Employment Practices Act, California has adopted a civil rights act which provides that all persons within the State of California, no matter what their race, color, religion, ancestry or national origin, are entitled to full and equal services in all business establishments of every kind whatsoever.

For any violation of this Act, a person will be liable for actual damages incurred by the injured party, plus an additional amount of $250. The California Court of Appeal has held that this Act is applicable to the practice of medicine and the services rendered by a physician.

Prohibition Against Discriminated Employment Practices Based on Sex

California also has a statute prohibiting discrimination, as between employees of the same classification, upon the basis of their sex. This statute forbids paying an employee of one sex at wage rates less than the rate paid the other sex for the same work in the same establishment. Violation of this law constitutes a misdemeanor and subjects the employer to civil liability to the employee.

Medical Economics

The Health Care Dollar

Some Factors Affecting Costs and Value Received

HOMER C. PHEASANT, M.D., *Los Angeles*

HEALTH CARE is probably the biggest industry in the United States, exceeded only by government workers in numbers of people involved. The combined worker aggregate of the automobile, aircraft and steel components of the national economy is less than that of the health care industry.[1] Looked at another way, medical care is a service industry which requires a large number of people to provide optimal health benefits. The cost of services is largely represented by salaries, and it is true that, at this time, the service component of the Consumer Price Index is rising faster than other components.

Distribution and Source of Health-Care Money

Studies vary somewhat as to distribution of the health-care dollar. Two sources, Hewitt Associates[2] and the *1966 Source Book of Health Insurance,*[3] roughly apportion 90 percent of the national health-care dollar to hospital services, physician and other professional services, and to drugs and appliances. Just under 30 percent of the health-care dollar goes to physicians for their professional services (Chart 1). Where does the money come from? Sixty-five percent comes from private sources. Thirty-four percent comes from public sources, with this percentage steadily increasing.

Health insurance has rapidly expanded and serves an increasing percentage of our national population (Chart 2).[3] This is in part due to organized labor's very proper concern for the health needs and care of members. While this degree of market penetration is a good sign, not all insurance policies are good, since they tend to vary

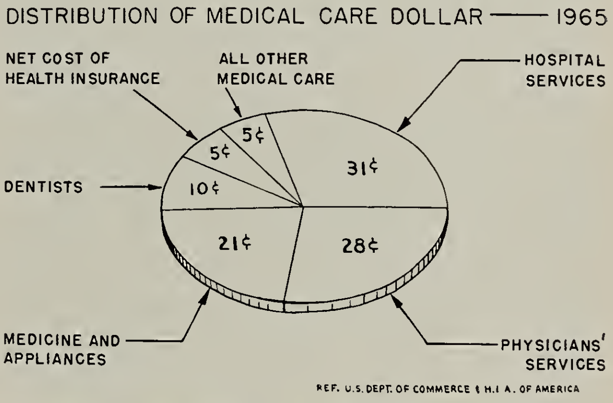

Chart 1.—Distribution of Medical Care Dollar in 1965.

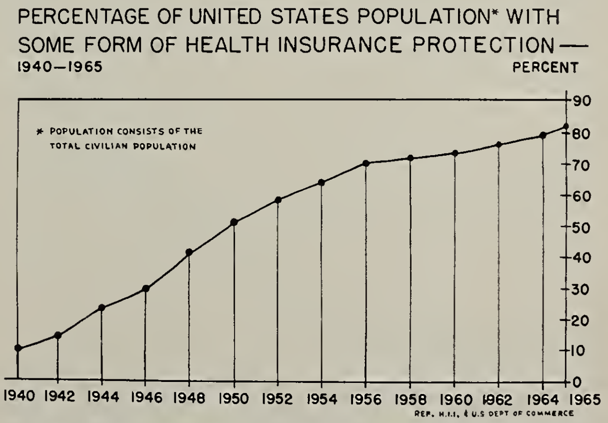

Chart 2.—Percentage of total *civilian* population with *some* form of health insurance.

Submitted, revised, 31 October 1968.
Reprint requests to: 2300 South Hope Street, Los Angeles 90007.

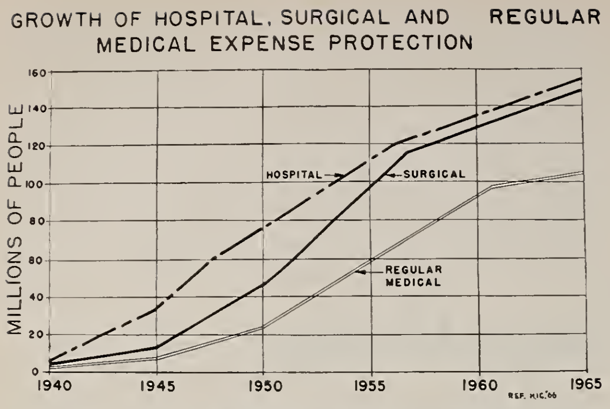

Chart 3.—Comparison of degree of market penetration of policies providing hospital, surgical, and regular medical expense protection.

rather widely in the scope of benefits they provide, and medical expense protection still lags between hospital and surgical coverage (Chart 3).[4] Some programs do not include adequate deterrent against abuse, and may, because of limitations in coverage, encourage abuse such as overuse of hospitalization for purely diagnostic services. At this time there is considerable talk of "first dollar coverage." Any first dollar coverage entails a large expense for claim processing. Twenty-six percent of health cost expenditures are accounted for by 60 percent of our population who have yearly medical bills of less than $100. It does not appear unreasonable that most individuals who have health insurance as part of a fringe benefit or as an individually purchased policy, could afford a $100 a year deductible coverage. As people obtain greater security against the unpredictable expense of illness or accident, the rate of utilization of medical services, both in the physician's office and in hospitals, increases. The inclusion of a deductible provision in all policies appears to make fiscal sense, not only by effecting some controls of over-utilization, but also by lessening administrative expenses.

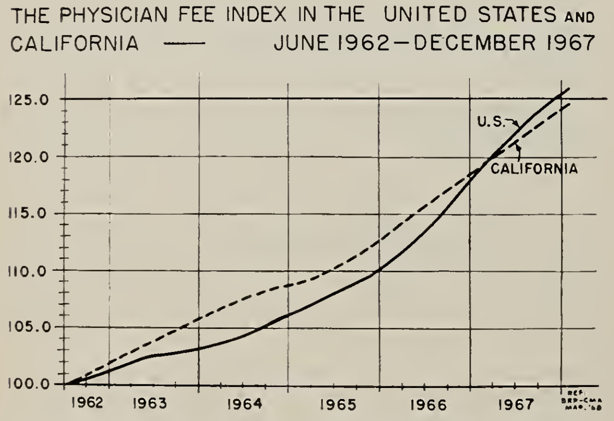

Chart 5.—The physician fee index in the United States and California—June 1962 - December 1967.

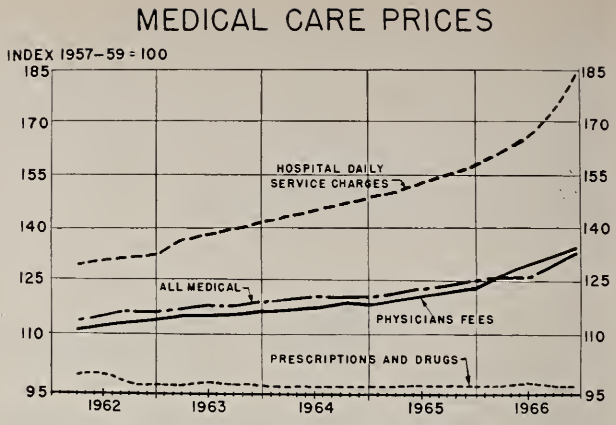

Chart 4.—A comparison of the increase in hospital charges compared with physician charges. (Note that in 1966 alone hospital costs rose 12 percent whereas physician fees showed the same increase as in preceding years, 5 percent.)

Physicians' control over the hospital cost of illness is limited. It is true that they do have appreciable control over hospital utilization, but they have practically no control over gross hospital charges, 65 percent of which are related to personnel salaries. Hospital costs have increased more rapidly than physicians' fees[2] (Chart 4). More important is the fact that hospital prices have increased 41 percent from 1962 through 1966, a five-year period, while physicians' fees have increased 18.8 percent during that time, that is, at an annual rate of less than 4 percent. Figures compiled by the Bureau of Research and Planning of the California Medical Association bear out the fact that the long-term increase rate in physicians' fees in California has been approximately the same as that indicated for the total United States. Within the past two years, however, there are indications that the rate of increase has been somewhat lower in California than in the nation, according to the Bureau's findings. (Chart 5.)[5]

Some critics combine the average of physician and hospital costs as an index of cost of medical care. This is misleading, because such grouping provides only a mean index of medical costs and doesn't separate the components. Other critics of the medical profession relate physicians' fees to the Consumer Price Index. This method of comparison is not entirely valid, since no index includes a device for measuring quality improvement. The likelihood of quality improvement in medical care can only be measured by the *"greater probability*

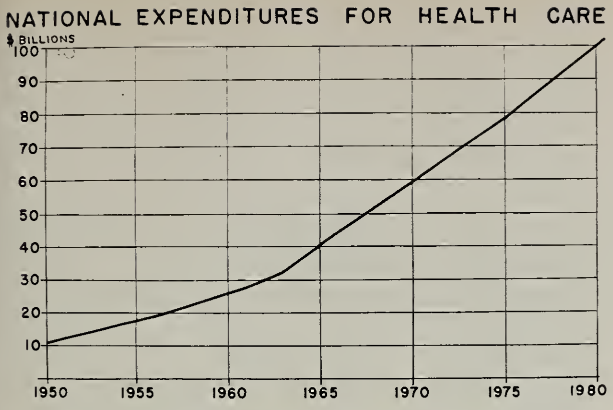

Chart 6.—Health care expenditures projected to the year 1980.[2]

today that an individual's health will benefit from a physician's service."[1]

There is no question that medical costs are increasing. The average medical expense of a family unit of four, including dental care, was almost $400 in 1965 and it is estimated that this will approach $750 in 1975. By the year 1975 national health expenditures will probably be in excess of $70 billion. By 1985 it is varyingly estimated that these costs will be between $110 billion and $122 billion (Chart 6).

Analysis of Cost Increases

Now, one may properly ask, "Why this increase?" One factor is the increased time spent with the patient which is necessary for a better patient-physician relationship and to improve medical care. Statistics are not available to permit objective appraisal of the hypothesis that present-day medical practice is not only technically more difficult and time-consuming, but must also relate to the changing social environment. Patients expect more from their physicians, and are also quicker to sue the physician and hospital. One cannot be both efficient in time-saving and still devote the appropriate time with patients that today's standards of care demand.

Let us analyze some of the other factors which brought about the increase in medical expenditures between 1950 and 1965.[2] Chart 7 shows that there are a number of additional components in the 1965 medical cost column which reflect not only the obvious, such as population increase, general inflation, and—much as one may dislike the term—"medical care inflation." But there is also an appreciable element in this increase which is related to greater use of services, the availability of new services due to advances in medical technology, the effect of the increased average age of the population, and the availability and accessibility of medical care and facilities.

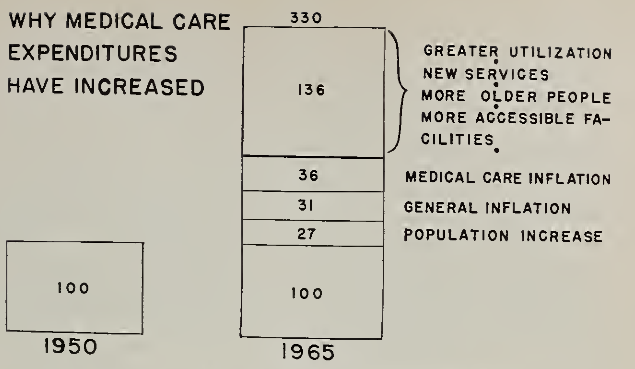

Chart 7.—Why medical care expenditures have increased.[2]

What Does the Future Hold?

There is an obvious need for all elements of the medical care industry to cooperate in an effort to improve efficiency of operation without lessening in any way the quality of medical care. Can physicians profit by improved office design, by the best use of modern facilities and equipment, by the best possible use of assistants and aides, and by the proper use of modern production and design engineering?

Should hospitals be massive and expensive monuments to organizations or individuals when medical technology is advancing so fast that even the most modern hospital becomes virtually obsolete after 15 years or so? Should we not consider a change in attitude about hospital construction? Why not accept in-built obsolescence and effect first-dollar cost savings so that we can rebuild hospitals every 15 years?

Should not hospitals operate completely and fully for six, or even seven days a week, through cooperation with organized medicine? Physicians and hospital personnel could stagger their on-duty and off-duty time to permit an expanded work-week of this type. This would decrease, if not eliminate, the present invariable decline in weekend hospital occupancy, would shorten length of stay, and would also accomplish economies in other areas of hospital operation. Such a plan has been successfully tested.[6]

The medical profession's answer to criticism should not be defensive, nor should it imply that further escalation in cost is totally beyond control and inevitable. Physicians can be constructive and attempt to identify areas where runaway costs can be controlled. Under optimal circumstances, improving the efficiency with which medical care is provided could reduce costs or at least hold them constant for some period. Is it imprudent to suggest that hospitals might even become competitive —not in bricks and mortar, cobalt therapy or open-heart surgery—but rather in efficiency and economy both in construction and operation? This could then be reflected by a lower per diem charge. Certainly physicians and hospitals must work together to implement those changes which would lessen cost yet maintain or improve the quality of care provided. There are those who feel that the social economics of the medical care industry are hopelessly obsolete. Some of these critics recommend change[5] which could be detrimental to the quality of care. If planning is left to government, one can foresee further manpower drains on already limited personnel resources. It is not too late for medicine to become productively involved in this problem, but not much time is left.

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CERVICAL EXTENSION OF ENDOMETRIAL CARCINOMA

"Since 1958 we have combined radiation with radical surgery in patients [with endometrial carcinoma] in whom fractional curettage has demonstrated cervical extension; and this has constituted approximately 15 percent of the patients treated. . . . In the remaining group where fractional curettage has not demonstrated cervical extension, we have not utilized intravaginal radiation — either therapeutically or prophylactically. In going over the material from 1958 through the present, we are pleased to report that we have not had a single recurrence in the vaginal wall in either series.

"This suggests to us that perhaps by utilizing a fractional curettage as a routine diagnostic measure in the evaluation of women with endometrial carcinoma, you may have a measure of being more selective in the patient who is going to receive routine intravaginal radiation. It's of interest, I think, that the more or less conventional incidence of so-called vaginal cuff recurrence — approximately 15 percent — is quite comparable to the incidence of cervical extension in endometrial carcinoma."

—JOHN G. MASTERSON, M.D., Chicago
Extracted from *Audio-Digest Obstetrics and Gynecology,* Vol. 15, No. 22, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

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California Medicine

EDITORIAL

Oversell and Undersell

THESE ARE TIMES of much ado about continuing education for physicians. There is an uncomfortable feeling abroad that progress in medical science is pulling way ahead of the practicing physician's ability to keep pace with it, and that this gap may impair the quality of patient care. The public's apprehension that this may be true is fed in many ways. For example, news media frequently give dramatic national, even worldwide coverage to items which are being reported for the first time at some scientific meeting and which have yet to be subjected to critical scrutiny or even confirmed. On the academic side, deans of medical schools and professors, who often practice little if at all, make authoritative statements to the effect that the half-life of a medical school education may now be only five or ten years at best because of the great progress which has been made in the laboratories of modern science.

The public understandably assumes that information emanating from respected scientific sources such as these is factual and complete and begins to wonder what must be the state of learning of a physician who has been out of medical school and in practice for 10, 20 or even 30 years. For these, and no doubt other reasons as well, the public is becoming concerned; and the feeling in many quarters is that something more should be done to ensure the continuing competence of practicing physicians.

All of this seems to suggest that there may have been somewhat of an oversell of institutional scientific progress and a corresponding undersell of the continuing medical education which in fact goes on in day to day practice. For example, little is made of the important fact that individual physicians learn from their contact with patients and from first hand experience with cases of disease, injury or emotional upset. This is a continuing education process of profound importance which while it begins in medical school carries on throughout a lifetime of practice. It gives rise not only to an important and cumulative body of professional knowledge, but also to things called wisdom and judgment, and to a curious capacity to make reasonably sound decisions on the basis of less than adequate data when time is an important factor or when the scientific information is simply not available. This experiential educational process also accounts for the fact that it is not unusual for practicing physicians to sense the value, or lack of value, of some new technologic discovery long before the scientific evidence accumulates to substantiate their clinical impression. It therefore seems obvious that the knowledge and skill derived from experience in practice is fully as important in patient care as is the up-to-dateness of scientific and technologic credentials which is now so in the forefront of public concern.

It should also be pointed out that the practicing physician is the target of a massive ongoing educational enterprise, and this also is not given its proper weight in the forming of what appears to be a general public opinion. The belief that private or "solo" physicians practice in isolation, with no contact with other physicians or with medical progress, somehow receives fairly wide acceptance, but it is simply untrue. The vast majority of practitioners work daily with other physicians, exchanging information and experiences. While this is an informal educational process, it is both practical and effective. More formal continuing education under professional auspices comes to each of the 23,000 members of the California Medical Association weekly through the *Journal of the American Medical Association,* and monthly through CALIFORNIA MEDICINE and an AMA specialty journal of his choice. Furthermore, every practicing physician is invited to dozens of meetings and more or less formal courses each year which are offered at medical centers or by professional associations, and each receives hundreds of communications of commercial origin which also strive to bring the latest advances to his attention. All of this adds up to a remarkable system for quickly disseminating scientific and technologic progress to the practicing physician. If anything it may be faulted for trying to pass along too much rather than too little.

The growing interest in improving continuing education for practicing physicians is praiseworthy and the desire of the public to have more assurance that a practicing physician is indeed up to date is reasonable, and it must somehow be fulfilled. But let whatever criteria are to be established not ignore the actualities of continuing education for practicing physicians as these exist today. Both the oversell and the undersell in continuing medical education are at present distorting and confusing the issue which must be resolved to the public satisfaction.

Cystic Fibrosis of the Pancreas—New Clues to the Metabolic Riddle

THE EXACT METABOLIC LESION in cystic fibrosis has not yet been discovered. Approximately one of every 2,000 persons born in the United States is afflicted with this generalized disorder of exocrine glands, characterized by excessive mucus production and inability of the ducts of sweat glands to reabsorb sodium, chloride and potassium. Chronic pulmonary disease is responsible for most of the morbidity and mortality. A few of the patients succumb to abdominal complications—in some cases as neonates with meconium ileus, in others later in life as a result of intestinal obstruction or secondary to a characteristic biliary cirrhosis. Attempts to explain these striking and devastating clinical features have recently led to significant advances in knowledge, providing clues for the search for the metabolic defect in cystic fibrosis.

The excretory duct of eccrine sweat glands of cystic fibrosis patients is unable to reabsorb electrolytes normally; except for the hyponatremia associated with severe chronic pulmonary disease, liver disease or acute massive salt loss by sweating in these patients, serum electrolytes are in the normal range. Attempts to demonstrate an electrolyte transport defect in the kidney have been thus far unsuccessful and cystic fibrosis patients and their normal age-matched counterparts respond normally to dietary sodium restriction and injection of aldosterone.[1] Recently, however, a red blood cell sodium transport defect has been clearly demonstrated in patients with cystic fibrosis and their parents.[2] The pancreas also demonstrates an abnormality in water and electrolyte metabolism: Pancreatic secretions in cystic fibrosis patients without pancreatic insufficiency have a very high enzyme content and a very small content of water and bicarbonate.[3] Thus sweat gland, red cell, and pancreas all demonstrate abnormalities in membrane transport mechanisms.

Abnormalities have been found now at the cellular level in cystic fibrosis. Danes and Bearn[4] have demonstrated granules with metachromatic staining in the cytoplasm of fibroblasts from cystic fibrosis patients and their parents, who are all carriers of the recessive cystic fibrosis gene. These cells contain metachromatic granules, after growing in tissue culture for several weeks, which seem to occur in two different patterns—either large vesicles, or diffuse smaller granules. Individual families have either one pattern or the other, and a few families demonstrate no metachromatic staining of fibroblasts. These findings have suggested that there are varying degrees of expression of the cystic fibrosis gene, a phenomenon observed in the clinical picture of the disease, or that there may be genes at different loci that are capable of producing the same disease. The latter would imply that cystic fibrosis may be a genetically heterogeneous disease.

At present the metachromasia of fibroblasts in tissue culture may be used as a means of confirming the diagnosis of cystic fibrosis when it is suspected clinically, and for the detection of carriers. The detection of this fibroblast abnormality requires specialized tissue culture techniques over several weeks. Recent preliminary studies by Danes and associates with peripheral white blood cell cultures suggest that these readily available cells may be used to demonstrate metachromasia in cystic fibrosis families as early as three or four days after beginning tissue culture. This would represent a significant advance in the usefulness of these studies. Matalon and Dorfman[5] have isolated and fractionated the acid mucopolysaccharides from the metachromatic staining material in cystic fibrosis fibroblasts in tissue culture; they have found an increase in all of the acid mucopolysaccharides, hyaluronic acid, dermatan sulfate A, and chondroitin sulfate A.

Metachromatic staining of fibroblasts has been found now in a list of more than 20 hereditary diseases. In a few of these diseases the metachromasia has been shown to be due to a specific increase in one or another of the acid mucopolysaccharides—for example, in Marfan's syndrome there is an accumulation mostly of hyaluronic acid. In cystic fibrosis, there appears to be a diffuse accumulation of all of the normal acid mucopolysaccharides. Although it is possible that the observed metachromasia exists in the lysosomes of these cells, this has not yet been confirmed. The reason for the accumulation of metachromatic material in cystic fibrosis cells remains unknown. Possible explanations include a deficiency of a lysosomal enzyme, or a deficiency of an enzyme outside lysosomes, leading to failure of degradation of the stored materials. In view of the other abnormalities found in membrane transport mechanisms in cystic fibrosis (sweat gland, red cell and pancreas), a more likely explanation might be the existence of an abnormality in lysosomal membranes, perhaps in their ability to transport mucopolysaccharides. This abnormality could be either a primary defect in the membrane itself, or the result of the metabolic derangement of an enzyme system normally involved in membrane transport.

Over the past two years "factors" have been described in the blood, sweat and saliva of cystic fibrosis patients, which appear to have important effects on membranes. Spock and associates[6] discovered that serum from cystic fibrosis patients has the ability to disorganize the normal rhythmic beat of the cilia of rabbit tracheal slices maintained in tissue culture. The sera from all parents of these children had the same activity when they were concentrated by precipitation of the euglobulin fraction. This serum factor is non-dialyzable and is heat-labile; it has not yet been isolated and characterized. Mangos and associates[7] have found a sodium transport inhibiting factor in the sweat and saliva of patients with cystic fibrosis which is not present in these secretions from normal persons.

This factor is associated with a 20,000 to 30,000 molecular weight fraction of these secretions, is characterized by a net positive charge, and is most likely a small protein or a polypeptide. It has not yet been isolated and characterized. This basic material may exert its effect on negatively-charged cell membranes in sweat and salivary ducts and alter their permeability to sodium, inhibiting the reabsorption of sodium in these ducts. Recent studies suggest that this factor may be induced with drugs or food intake in normal persons. Initial studies for molecular weight suggest that the serum factor is of much larger size than the factor in sweat and saliva. It is possible that the factor in sweat and saliva is related chemically to the serum factor and is either bound to a carrier molecule in serum or is actually part of a large serum protein molecule.

Biologically-active peptides are known to circulate as integral parts of serum protein molecules in the complement, kinin, clotting, and angiotensin-renin systems. These peptides are released in the circulation or in tissues by the action of specific enzymes which are either activated directly in the circulation or released from tissue into the circulation as the result of tissue injury. One of these peptides, or some other thus far uncharacterized basic peptide, may be involved in the pathogenesis of the membrane transport abnormalities demonstrable in cystic fibrosis.

In addition to its abnormalities in membrane transport of electrolytes, cystic fibrosis is characterized by an excessive mucus production throughout the body. Extensive research has demonstrated only an increase in macromolecular components normally present in the mucous secretions but no unique abnormal glycoprotein molecule.[1] It is possible that the excessive mucus is indeed a result of the defect in membrane transport, but this remains to be substantiated.

In spite of these helpful new clues, the metabolic riddle of cystic fibrosis remains unsolved. When the factors which can influence metabolism of electrolytes or of glycoproteins or both have been clearly identified, one must ask whether their presence is the result of a missing enzyme which normally degrades them, or of a missing normal inhibitor, or of a genetically-determined overproduction of a normal substance. Spirited collaboration of geneticist, biochemist, physiologist, immunologist and clinician will be required to follow the present promising clues to their final answer.

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Bone Disease in Chronic Renal Failure — Questionably the Result of Our "Successful" Treatment of Uremia

THE LAST FEW YEARS have seen a remarkable increase in the clinical investigative interest in the disordered divalent ion metabolism and bone disease associated with chronic renal failure. This increased interest is directly related to the fact that as the lives of patients with this disorder have been greatly prolonged by transplantation, clinically severe osteodystrophy and soft tissue calcification have become life-threatening problems in an alarming number of cases. It is deeply distressing that we are able to treat uremia successfully and to rehabilitate the patient only to be confronted, at times, with the most florid forms of metabolic bone disease, and a type of vascular and soft tissue calcification capable of causing severe ischemic necrosis of skin, subcutaneous tissue, and phalanges. We and others have observed that as the duration of chronic dialysis increases, regardless of the composition of the dialysate, the frequency of bone disease and soft tissue calcification also increases. In our own series the incidence of radiological evidence of bone disease increased from 18 percent at one year to 92 percent at the end of three years. This is not an unusual experience in major dialysis centers.

Despite these pessimistic observations it is clear that the recent acceleration in clinical and laboratory investigation into the problems of renal osteodystrophy are bringing us closer to a proper understanding of its cause, diagnosis and treatment. The present issue of CALIFORNIA MEDICINE contains Dr. Frank Muldowney's review entitled "Metabolic Bone Disease Secondary to Renal and Intestinal Disorders." Dr. Muldowney has given us an example of the type of challenging and provocative concepts and inquiries now being made in this field. He discusses the similarities and differences between the biochemical changes and metabolic bone disease of chronic renal failure and those of intestinal disorders associated with calcium, phosphorus and vitamin D deficiency. He suggests that phosphate depletion, which may be common to

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Supported by U.S. Public Health Service Contract No. 43-68-1040.

both, may be the fundamental cause of the osteomalacia component of renal osteodystrophy, while the osteitis fibrosa component is due to the prolonged (years) secondary hyperparathyroidism. Dr. Muldowney suggests that the hypocalcemia responsible for the parathyroid hyperplasia in chronic renal failure is due to small but progressive increments in serum inorganic phosphorus, which in turn are secondary to a gradual reduction in glomerular filtration rate (GFR) and renal mass. It is quite clear that renal osteodystrophy represents a varied histologic picture with osteomalacia and osteitis fibrosa predominating, but frequently with varying degrees of true bone atrophy (osteoporosis) and ostesclerosis also present.[1] Furthermore, the clinically and histologically (bone biopsy) predominant lesion in any given patient may vary depending on the age of the patient, the duration and severity of his renal failure, his long-term nutritional state and the nature of his treatment, including, of course, chronic dialysis.[2] In fact, one form of therapy may tend to correct or ameliorate a given skeletal lesion, while aggravating another. For example, "very successful" large-dose antacid therapy may lower serum phosphorus to normal and thereby at times return serum calcium to normal. The latter may decrease the pronounced hypersecretion of parathyroid hormone and lessen the degree of osteitis fibrosa or parathyroid bone disease. Antacid therapy lowers serum phosphorus by inhibiting the intestinal absorption of phosphorus and causing phosphorus depletion. The latter, as stressed by Dr. Muldowney, can aggravate or cause osteomalacia, with a failure of available bone matrix to mineralize.

Bone atrophy, or osteoporosis, when present may be due to aging, chronic calcium and protein deficiency, plus varying degrees of inactivity. It should be stressed that the therapeutic diet of the azotemic patient is almost always deficient in calcium, phosphorus and protein. The exact cause of osteosclerosis (hyperostosis, per Dr. Muldowney), or more mineralized bone per unit volume,[1] is unknown. It may represent aberrant calcification of excess osteoid or the fibrous matrix of osteitis fibrosa. If in any given patient with chronic renal disease it was possible to study the entire skeleton, varying amounts of each of these histologic lesions would be seen.

It is becoming increasingly clear that the abnormal metabolism of divalent ions and metabolic bone disease may begin very early in patients with chronic renal disease. Minimal reductions in glomerular filtration rate may be associated with hypocalciuria, defective absorption of calcium from the gastrointestinal tract, slight hypocalcemia with normal, or even low, serum phosphorus,[3] and a relatively high renal clearance or low tubular reabsorption (TRP) of phosphorus.[3] This is the classic biochemical pattern produced by a vitamin D deficient or resistant state with secondary overactivity of the parathyroid glands. In confirmation of the latter, elevated levels of parathyroid hormone, as measured by radioimmunoassay, have now been detected in the plasma of patients with less than 20 percent reduction in GFR.[4] Unfortunately, information on bone histology and the biochemical response to vitamin D in these early cases is not yet available.

Although Dr. Muldowney has emphasized the role of phosphate depletion and early small increases in serum phosphorus as playing fundamental etiologic roles in osteomalacia and osteitis fibrosa in chronic renal disease, the overall evidence seems to be more in favor of the early development of an acquired vitamin D resistant state which in turn is responsible for: (1) impaired absorption of calcium from the gastrointestinal tract; (2) defective mineralization of osseous matrix, or osteomalacia; (3) impaired response of the skeleton to parathyroid hormone. It has been clearly shown experimentally[5] that a vitamin D effect on the skeleton is essential for the normal response of the latter to parathyroid hormone. Therefore, a greater amount of parathyroid hormone is necessary to maintain a normal serum calcium. Factors 1 and 3 would be primarily responsible for the early development of hypocalcemia *in the absence of* hyperphosphatemia. However, as was emphasized by Dr. Muldowney, any rise in serum phosphorus would tend to lower the serum calcium further. As long as the latter is maintained, hyperplasia and hypersecretion of the parathyroids will continue. After many years the parathyroid glands may enlarge as much as 50 to 100 times, and the circulating levels of parathyroid hormone may exceed 1,000 times the normal concentration.[4] Osteitis fibrosa appears in a florid form, serum calcium returns to, or even goes slightly above, normal; and due to the simultaneous hyperphosphatemia the $Ca^{++} \times PO_4^{\equiv}$ product attains a level where soft tissue calcification is inevitable. At this point the parathyroid glands are so massively enlarged that they continue to secrete excessive amounts of hormone despite normocalcemia, and if hypocalcemia develops again these huge glands secrete much more hormone than normal for any given degree of hypocalcemia. It is probable that true autonomy of the parathyroid glands does not exist in chronic renal failure, the apparent autonomy being simply the result of the mass of secreting parathyroid tissue.[6] However, when this "autonomous" state does exist almost all forms of therapy, short of subtotal or total parathyroidectomy, may either aggravate the bone disease or decidedly increase soft tissue calcification. We are then confronted with the complete picture of severe sustained secondary hyperparathyroidism in chronic renal failure—that is (1) serum calcium usually normal, rarely elevated; (2) hypercalcemia after phosphate restriction; (3) hyperphosphatemia, which may respond poorly to phosphate restriction or hemodialysis; (4) osteitis fibrosa or subperiosteal bone resorption; (5) soft tissue calcification; (6) increased calcium content of skin; (7) pruritus unresponsive to adequate dialysis; (8) postdialysis diffusible or ionized calcium in serum greater than its concentration in the dialysate; (9) elevated alkaline phosphatase, or (10) bone pain (uncommon).[6]

It was pleasant to note Dr. Muldowney's discussion of magnesium depletion in humans and its possible role in impairing the end organ response to parathyroid hormone, and the ability of mild hypermagnesemia to inhibit parathyroid secretion.[7] While we have stressed the role of the vitamin D resistant state as the fundamental "lesion" contributing to the early over-activity of the parathyroid gland, it is possible that magnesium deficiency could have the same result.

It is clear from Dr. Muldowney's and the present discussion that the clinician confronted with a disordered divalent ion metabolism and bone disease in chronic renal failure must make the most critical evaluation before proceeding with any specific form of therapy. One approach may improve a given biochemical abnormality while leading to a further deterioration of the skeleton or more soft tissue calcification.

As in all research or clinical investigation, as an increased number of clinicians and investigators become involved in gathering data and searching for the correct answers, the contributions increase in a geometric manner and it is that we are now at this phase. It seems likely that the most important answers with respect to the pathogenesis, diagnosis and treatment of these serious disorders will be available to us very soon.

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Medicine and the New Human Condition

THE HUMAN CONDITION seems to be undergoing a change. The cause is easy to understand. The energy of man's machines is doing much of the work which used to require his muscles, and a lot more. This has happened only recently. The result seems certain to be a truly new human condition to which human beings must adjust.

A curious paradox has developed which may be one of the root causes of many present day tensions. On the one hand inanimate power has reduced the need for human or even animal labor. Leisure has increased and affluence is unprecedented. A new expectation, even a demand for the opportunity of self-expression and individual fulfillment has become an insistent force in our society. There is real restiveness when these expectations and demands are not instantly met. On the other hand the refinements of scientific and technologic progress which make this very human dream seem so close to attainable exact their price. The more it frees of man's time, muscle and intellect the more it demands from him of collaboration, coordination, planning, regulation and even control if the complex technologic society which permits of this new freedom is to improve rather than destroy the quality of human life.

This paradox of the new human condition is clearly seen in health care. Scientific achievement and the expectation of even greater technologic progress have led to upgrading of the very idea of health until now it is becoming viewed as a state of well-being, even of personal fulfillment, rather than simply the absence of disease. And the more successful the health care system becomes the greater are the problems, the expectations, the complexity of the services, the higher the costs, and the more of organization, regulation and control that is required. And again, accompanying this technologic progress there is destined to be increasing human dependence, dissatisfaction and even restiveness. It seems that this paradox is real and that it will be an important characteristic of the human condition for the foreseeable future.

In a very real sense this is as much a biological phenomenon as it is anything else. Individual fulfillment is a biologically sound concept. It is an idea physicians can understand and accept. It is as old as the healing arts. And so is the paradox which now plagues the human condition. The health and well-being of anyone has always depended upon one's satisfactory adjustment within one's constraints, be they physical, emotional, social, economic, cultural or even political. Physicians have always sought to restore and maintain health and well-being within this framework. Diagnosis, treatment, prevention and rehabilitation are the tools a physician uses to improve this adjustment, whether by strengthening the individual, manipulating the environment or improving the character of the adjustment. This is the realm of medicine which must now develop its technology to deal with the new human condition much as it has with the old.

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LETTERS *to the Editor*

Whose Momism?

To the Editor: Your praise of the review of the book "Fear of Women" (Calif. Med., 110:280, March 1969) was well merited. The reviewer's final verdict on the book could well apply to the review—it's a gem.

I have one small quibble, however. Dr. Miller says "Momism is portrayed in a less humorous manner than Huxley's, etc." Didn't he mean Philip Wylie's, in "Generation of Vipers?"

ABE CLINE, M.D.
2741 Royal Crest Drive
Escondido

• *The author of the book review in question says that he is not certain who invented the epithet "Momism"—Wylie it may be—but he is sure he has been entertained by Huxley's treatment of the subject.*

Family Life Education—What's Behind a Name?

To the Editor: The health and family life programs have received a great deal of attention in the past few years and would appear to answer a need in the training and development of young people. As physicians we need to scrutinize the classes carefully, as our recommendations will influence in greater or less degree the reception of this type of education by the community at large. We all agree on the goal of passing on attitudes and values to the younger generation through this program, but until we objectively evaluate its results, our opinion is really of no more value than that of any other sincere, responsible citizen, whose opinion is based on beliefs and feelings. We may rightly ask what objective criteria can be used to measure the value of the family life program, and I believe such criteria should be developed, and then a controlled study set up to gather data and reach sound conclusions, as in any field of medicine. In this way we will be truly performing in our role as physicians in the community, bringing to this problem the benefit of our training, knowledge, and experience in an unprejudiced manner for the benefit of community health.

These remarks apply to the family life programs, as they presently encompass personal development and adjustment, necking and petting, adolescence and puberty, marriage preparation, dating, courtship, attitudes toward sex, moral values, child-parent relationships, and solving real life problems. It is agreed that it is our duty to try to teach to youngsters sound attitudes and values which we as adults know are essential for effective living and personal development. Whether the family life education program will do this or not is not really known, we must honestly admit.

Although experience elsewhere is not necessarily valid for our society, it is still worthwhile noting that in Sweden where education about sexual intercourse and contraception is taught in the schools beginning in the equivalent of our sixth grade, 98 percent of the married population have intercourse before marriage and every seventh child is born out of wedlock. Likewise the venereal disease rate has increased alarmingly. There can be little doubt in most of our minds that these two events in the life of a teenager represent calamities and difficulties that may haunt them later. Possibly studying the incidence of these two health problems (i.e., premarital pregnancy and venereal disease) in communities with and without a family life program would be one way of making the objective evaluation referred to earlier.

We should also pay some attention to what the authorities in the field of sex and family life education have said in regard to what can be accomplished through the programs. John Gagnon of the Indiana University of Sex Research and active in this educational field, said (in the Saturday Review of Nov. 18, 1967), "Few people take seriously the assumptions that sex education will lower rates of illegitimacy, venereal disease, or promiscuity (whatever that might be)." Lester A. Kirkendall, Oregon State University professor of Family Life and active in a consulting position with school curriculum personnel, was asked if the program would reduce premarital sex and venereal disease. His reply was, "To be perfectly blunt about it, we have no way of knowing that sex education will solve any such problems." (Reader's Digest, June 1968).

With parents and local educators asking what can be done about the increasing prevalence of social ills, it would seem that the leaders in the field of human sexuality are not trying to give solutions, and indeed are not able to do so. If it is believed at the university level that family life education will not and need not be expected to solve these pressing problems, why are we supporting the local programs, which are formulated and taught by teachers who themselves have been educated in this approach toward the whole field of family life? We can see that the controversy over whether the program is called sex, health or family life education is irrelevant, as actually the content in any case will be the same, as long as it is guided by the same philosophy.

Let us then be discriminating in our approval of health programs, and emphasize the importance of what we *know* can be accomplished through giving certain information to youth. For example, the greatest venereal disease incidence in Los Angeles County is now among adult heterosexuals, while there has been a decrease in teenage cases. This trend has followed the institution of an excellent venereal disease information program in the schools. A strong program of this kind should have our full support, along with instruction at appropriate age levels in the anatomy and physiology of human reproduction. It would seem far more responsible to broaden the school curriculum in areas of proven educational value and need, rather than advocate innovation of a program of unproven value which may offend some responsible religious groups in our population and require additional commitment of tax monies.

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DRUG-INDUCED MEGALOBLASTIC ANEMIA

"In the presence of glucose-6-phosphate dehydrogenase deficiency, which occurs in three percent of Negro gravidas, it's possible for the administration of nitrofurantoin (Furadantin) and other nitrofurans, as well as chloramphenicol and sulfonamides, to induce megaloblastic anemia. This is an additive factor. The increased demands for folic acid within pregnancy, perhaps the deficiency accompanying nausea and vomiting — these factors combine with the use of these drugs; and nitrofurantoins seem to act similarly to diphenylhydantoin (Dilantin) in being able to bring about a megaloblastic anemia."

—WILLIAM A. LITTLE, M.D., Miami

Extracted from *Audio-Digest Obstetrics and Gynecology,* Vol. 15, No. 23, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

Information

Aspirin and Gastrointestinal Bleeding

An Opinion

RICHARD R. BABB, M.D., AND
RICHARD S. WILBUR, M.D., *Palo Alto*

IN OUR EXPERIENCE, aspirin* is a common, and often overlooked, cause of gastrointestinal bleeding. Failure to question the bleeding patient with regard to aspirin ingestion can lead to costly, difficult and often dangerous diagnostic and therapeutic procedures.

Many studies[1-21] have shown that the majority of healthy persons who ingest aspirin-containing compounds in therapeutic doses will bleed in varying amounts. Although the amount lost into the gut is usually less than 6 ml per day,[15-20] some persons have lost more than 100 ml. In general, the bleeding has occurred whether the aspirin is in tablet, soluble or "buffered" form,[7,9,11,13,16-18] There have been case reports of patients with unexplained chronic blood loss anemia, who were "cured" when chronic aspirin ingestion was stopped.[22-24] We have recently seen two such patients, for one of whom exploratory surgical operation had been recommended.

Aspirin ingestion is also important as a cause of acute gastrointestinal bleeding. In a number of reported series[1,2,4,5,9-11,21,23] retrospective analysis has shown an incidence of aspirin ingestion during the preceding 48 hours in anywhere from 12 to 70 percent of patients with acute upper gastrointestinal hemorrhage.[1,2,4,5,9-11,21,23] In a prospective study over the past three years of 125 patients with acute upper gastrointestinal bleeding, we have found that 102 (80 percent) had taken aspirin in the preceding 48 hours. About 75 percent had taken from six to 12 tablets of 5 grains each in that time and had had no other medication. Only seven of 50 consecutive patients who were admitted to hospital for other reasons, and only eight of 32 roommates of bleeding patients, had taken aspirin-containing compounds in the 48 hours preceding admission.

The diagnostic studies in the bleeding patients were directed by a large number of primary physicians. However, in 78 cases it was possible to identify a likely source of bleeding such as peptic ulcer or hiatal hernia, stomach cancer, or varices. In 62 of these 78 cases the patients had ingested aspirin, which may have aggravated the bleeding. Of the 47 patients without an identifiable bleeding lesion, 40 had taken aspirin, and in those cases the drug must be suspected of being a primary or an important secondary cause of a hemorrhagic gastritis.

The exact mechanism of aspirin-induced bleeding remains uncertain. Current theories include direct local irritation of the gastric mucosa,[1,2,9,12,25-27] increased rate of loss of gastric surface cells (exfoliation) leading to mucosal erosion,[28] disruption of the mucosal barrier with subsequent capillary damage by histamine and hydrochloric acid,[29,30] alteration in the quality and quantity of the gastric mucus,[31] faulty hemostasis secondary to impairment of blood coagulation[32,33] and inhibition of adenosine diphosphate release and poor aggregation by damaged platelets.[34,35]

Since over 20 million pounds of aspirin are sold each year in this country, it is obvious that most consumers do not bleed overtly. There are a number of possible reasons for this, including individual variability. The "susceptibility" to aspirin-induced injury may depend upon the previous condition of the gastric mucsosa,[27] gastric pH,[30,36] gastric motility,[29] gastric emptying time,[29] the rate of surface cell replacement,[28] the individual's coagulation mechanism, capillary fragility, the amount, nature, and dissolution rate of the ingested material,[1,2] the amount of food in the stomach, and other factors of unknown importance, including emotional and environmental. To this time, human and animal experiments have failed to answer these questions conclusively.

Since we know of no accurate method of predicting "susceptibility," we must consider aspirin potentially dangerous to anyone.

From the Section of Gastroenterology, Palo Alto Medical Clinic, Palo Alto. Submitted 17 February 1969.

Reprint requests to: Palo Alto Medical Clinic, 300 Homer Avenue, Palo Alto 94301 (Dr. Babb).

*For purposes of brevity, we have used aspirin to denote any compound containing acetylsalicylic acid. There are over 300 such drugs on the market.

We, therefore, conclude that:

- Aspirin is a common cause of both acute and chronic gastrointestinal hemorrhage.
- Patients with chronic blood loss anemia may be spared costly and possibly dangerous diagnostic testing if they are thoroughly questioned regarding previous aspirin ingestion.
- Patients with known potentially hemorrhagic upper gastrointestinal disease, and those who have had hemorrhages of unknown cause, should be warned to avoid aspirin.
- For patients who have had repeated episodes of acute hemorrhage associated with aspirin ingestion, surgical operation should not be considered until it has been determined that they have a tendency to bleed even when they are not taking aspirin.

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Cardioversion

BERNARD LOWN, M.D.

Material supplied by the California Heart Association

It is now six years since the introduction of cardioversion as a method for terminating arrhythmias. To date many thousands of patients have been successfully treated. This extensive experience provides an adequate basis for assessing the advantages and limitations of cardioversion. Ectopic tachycardias in the past have been controlled by means of drugs. The use of anti-arrhythmic agents, however, presents a number of limitations. To reach an effective dose requires a time consuming biologic titration involving frequent if not continuous monitoring of patients. However, whatever the precautions, serious side effects frequently occur. Furthermore, all anti-arrhythmic drugs when given rapidly or in large doses or when administered intravenously, depress myocardial con-

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Dr. Lown is from the Medical Clinics of the Peter Bent Brigham Hospital and the Cardiovascular Laboratories of the Department of Nutrition, Harvard School of Public Health, Boston.

tractility and reduce peripheral resistance. This may prove especially dangerous in the presence of an arrhythmia which already has compromised cardiac reserve.

Method and Rationale

The majority of human tachyarrhythmias are self-sustaining by virtue of recirculation of an excitable stimulus over a fixed or variable pathway. When the pathway is blocked, the ectopic mechanism is extinguished and the sinus node resumes its usual role as dominant pacemaker. Such block can be induced by an electrical pulse which depolarizes the entire heart and thereby abolishes momentarily all excitable activity. The hazard of electrical shock, namely, cardiac asystole and ventricular fibrillation, can be prevented by the use of brief direct current (DC) pulses and by discharging these pulses into a safe part of the cardiac cycle. The dangerous part of the cycle is the vulnerable period occurring at the time of inscription of the apex of the T wave. Electrical energy triggered into the heart during the vulnerable period results in ventricular fibrillation. Transthoracic DC shocks synchronized to discharge outside the T wave are both effective and safe for terminating a diversity of arrhythmias.

The Technique of Cardioversion

Since the most common disorder treated with cardioversion is chronic atrial fibrillation, the steps to be described apply especially to this arrhythmia. However, the same procedure with but slight modification is applicable to other ectopic mechanisms. In the case of elective reversion, the patient is started one to two days before the procedure on maintenance quinidine therapy in a dose of 0.3 gram (5 gr) 6 hourly. The objective of administering quinidine is four-fold: (1) to develop adequate serum and tissue levels in order to prevent prompt recurrence of the arrhythmia; (2) to determine whether quinidine is well tolerated; (3) to obtain a small dividend of reversions observed in about 10 percent of patients with chronic atrial fibrillation while on maintenance quinidine therapy; and (4) to diminish the incidence of ectopic mechanisms immediately following cardioversion. One hour before the procedure 0.1 gram pentobarbital sodium (Nembutal®) is given orally. Transient amnesia is achieved by use of diazepam (Valium®) given in a dose of 2.5 mg intravenously and repeated at two minute intervals until mild anesthesia. This drug is well tolerated and generally about 10 to 15 mg suffices for the desired effect. The two electrode paddles are coated with liberal layers of conductive paste and applied in a front-back orientation. The anterior paddle is held with pressure on the mid sternum while the patient lies on the posterior paddle which is located in the left infrascapular region.

Perhaps the most important aspect of the procedure is to begin with low energy settings of 1 to 5 watt seconds (WS) and then proceed with higher energies such as 25, 50, 100, 200, 300, up to 400 WS. The practice of energy titration protects against serious complicating arrhythmias. For example, if electric shock provokes ectopic beats at low energies before reversion is achieved, one has the option of postponing the procedure or else administering lidocaine in a bolus of 50 mg intravenously. If such titration is carried out, it is not necessary to discontinue digitalis drugs prior to cardioversion. The reversion itself takes but a fraction of a second and the patient is usually awake within a few minutes. When a normal mechanism is restored blood pressure generally rises. There is no need to monitor the patient for a period longer than one hour if the procedure is uncomplicated.

Selection of Patients

How are patients to be selected for cardioversion? Two questions need to be answered: (1) is the arrhythmia susceptible to electrical reversion? and (2) will a normal mechanism be maintained for a sufficiently long time? Cardioversion has no place in the treatment of brief paroxysmal arrhythmias, recurring ectopic beats or deranged atrioventricular or intraventricular conduction. It is without effect when the mechanism is sinus tachycardia, a reflex physiological acceleration of the normal pacemaker which does not yield to antiarrhythmic measures. Digitalis induced rhythm disorders similarly are impervious to cardioversion. Furthermore, in the presence of digitalis toxic arrhythmias, more serious and even fatal disorders of the heart beat may result.

A number of patients are poor candidates for cardioversion because though sinus rhythm can be established it cannot be maintained. When quinidine is not tolerated and adverse reactions follow procaine amide, a normal rhythm will not persist.

Patients with rheumatic heart disease who have been in continuous atrial fibrillation for more than two years or those with advanced degrees of mitral regurgitation who display a giant left atrium are unlikely to remain in sinus rhythm long enough to justify cardioversion. The elderly asymptomatic patient with coronary artery disease and atrial fibrillation who exhibits a slow ventricular rate prior to digitalization is an unsuitable subject. Patients who have recurrent paroxysm of diverse atrial arrhythmias should not be reverted once they develop atrial fibrillation. They are less symptomatic with atrial fibrillation than when in sinus rhythm punctuated by frequent paroxysms of tachycardia. Patients should not be reverted before, during, or immediately after valvular operations. It is preferable to wait for ten or more days after surgery since sinus rhythm is then more likely to be long lasting.

Overall Results

To date at the Peter Bent Brigham Hospital 900 patients have been reverted by means of cardioversion. Chronic atrial fibrillation accounted for 650 of these episodes; 150 had atrial flutter and the remaining 100 had either ventricular tachycardia or varying supraventricular mechanisms. The overall success rate was 95 percent. These results are the more impressive, since the arrhythmia in many of these patients had proved refractory to large doses of anti-arrhythmic drugs. More than 2,000 electrical shocks were employed; yet, there was not a single episode of prolonged cardiac asystole and but one episode of ventricular fibrillation due to a failure to synchronize the shock. Although many of the patients were in critical condition and a number had sustained acute myocardial infarction and were in far advanced stages of congestive heart failure, none died as a result of cardioversion. Serious immediate complications were limited to 10 episodes of ventricular tachycardia. These were of brief duration and readily controlled. Eight of the patients suffered systemic thromboembolic complications within 1 to 8 days following cardioversion.

Specific Rhythm Disorders

Atrial fibrillation is the most common chronic disorder of the heart beat. One is no longer justified in using quinidine for reversion of this disorder. With quinidine, even when given in large doses, only 50 percent of patients are restored to sinus rhythm; however, 30 percent experience significant toxic reactions and 1 to 2 percent may die from the drug. With cardioversion, atrial fibrillation can be terminated in more than 90 percent with an incidence of complications not exceeding 1 percent.

Immediately after the cardioversion discharge, there may be transitional mechanisms consisting of nodal rhythm, a shifting pacemaker, and ectopic atrial beats. These are observed in about 50 percent of patients and continue for 30 to 60 seconds until the sinus node "warms up." With restoration of sinus rhythm, the ventricular rate is slowed. The PR interval is generally full and not infrequently first degree heart block is present. The overall hemodynamic state is improved with a rise in cardiac output by about 30 percent. The most salutory effects are observed in patients who are afflicted with mitral and aortic valvular insufficiency. Maintenance quinidine therapy has to be continued in an adequate dose of at least 1.2 gram daily which results in blood level of about 3 mg per litre. Even with this dose of quinidine, atrial fibrillation will recur within 6 months in 50 percent of patients.

Atrial flutter is best treated with cardioversion. It is the easiest disorder to terminate electrically. The arrhythmia generally responds to a single low energy shock of as little as 1 to 5 WS. No serious complications have been encountered.

Supraventricular tachycardias often present complex diagnostic and therapeutic problems. Frequently, it is difficult to define the mechanism precisely whether it is of atrial or nodal origin. More important is to determine whether digitalis glycosides are responsible for the disordered rhythm. If the arrhythmia is due to digitalis intoxication, electrical shock may provoke lethal disorders of the heart beat. When, however, small energies are employed and lidocaine is used to abolish ventricular ectopic beats, the supraventricular arrhythmias can be safely treated with cardioversion. The success rate, however, is only 70 percent.

Ventricular tachycardia responds well to anti-arrhythmic drugs such as procaine amide and lidocaine and these constitute the preferred therapy. When the arrhythmia, however, is accompanied by significant hypotension, or the patient is in pulmonary edema, or the tachycardia has developed in the wake of acute myocardial infarction and does not yield immediately to a bolus injection of lidocaine, cardioversion should be employed promptly.

Complications

The major complication following cardioversion of chronic atrial fibrillation is systemic or pulmonary embolism. This occurs in 1 percent of patients who have not received anticoagulant drugs. If the reversion is elective and the underlying disease is rheumatic valvular, pretreatment with anticoagulants for two to three weeks is indicated. Aside from thromboembolism, atrial and ventricular arrhythmias may complicate the cardioversion procedure. The atrial mechanisms generally are of three types: (1) delayed warm up of the sinus node manifested by sinus bradycardia, nodal rhythm or escape beats—the so-called "somnolent sinus node syndrome," (2) increased atrial automaticity demonstrated by single or multiple atrial premature beats at times associated with brief salvos of tachycardia and (3) "sick sinus node syndrome," a defect in the elaboration or conduction of the sinus impulse characterized by chaotic atrial activity and usually followed by prompt re-establishment of atrial fibrillation.

The ventricular arrhythmias complicating cardioversion are less common but more threatening than the atrial disorders. These are of two types: ventricular fibrillation, which occurs immediately after delivery of the shock and usually is the result of improper synchronization; the second type develops after several beats or within a few minutes and consists of bigeminy or multifocal ventricular ectopic beats which may result in ventricular tachycardia or rarely in ventricular fibrillation. These later arrhythmias are generally associated with excessive digitalis. Lidocaine, in one or more injections of 50 mg intravenously, is promptly effective.

Conclusion

The method of cardioversion is simple and direct. The physician can observe the entire process of reversion. It does not require a great investment of physician or patient time and is applicable to diverse arrhythmias. Differentiation between ectopic disorders, essential in the use of drugs, ceases to be a critical requisite for effective therapy.

Cardioversion is not accompanied by significant occurrence of serious complications. There is no depression of contractility, conductivity or excitability of the heart—a common sequel after large doses of anti-arrhythmic drugs. The method of cardioversion can be readily mastered by the general physician.

RADIOTHERAPY IN LUNG CANCER

What would radiotherapy add to the drug therapy of lung cancer?

"The studies done so far have indicated that radiotherapy in the patient with disease that's encompassable by an x-ray field has not added significantly to survival. In fact, one study found that the use of cyclophosphamide (trade named Cytoxan) once a month is essentially equal to, if not better than, any advantage at all from radiotherapy. I think that the reason is fairly obvious. A lot of these patients probably have metastases outside the radiation field; they aren't dying of pulmonary problems, but of distant metastases. I think that radiotherapy is a good tool for the local control of specific problems in lung cancer."

—Paul P. Carbone, M.D., Bethesda

Extracted from *Audio-Digest Internal Medicine,* Vol. 15, No. 23, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

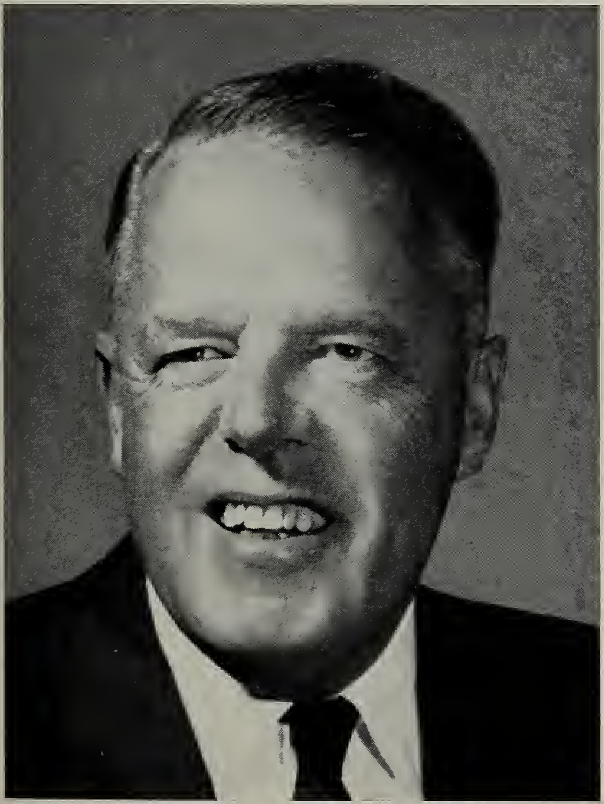
California Medical Association

New CMA Officers

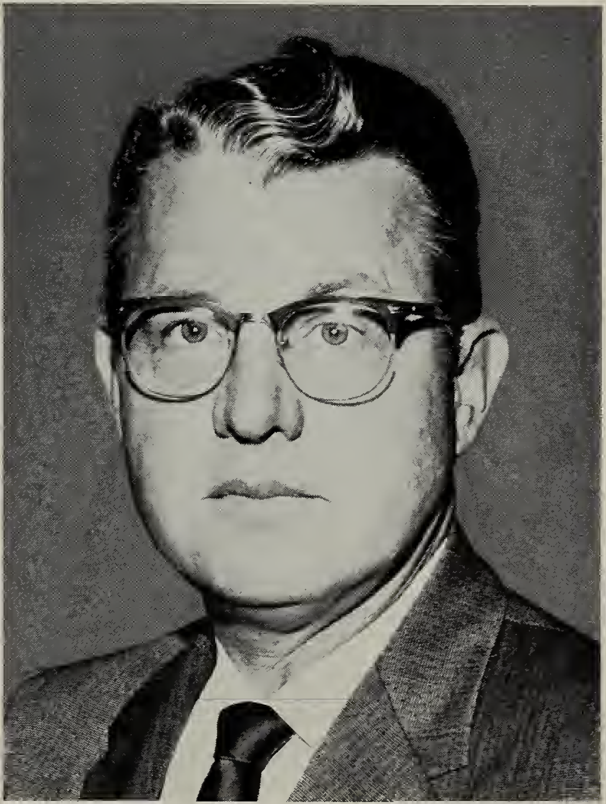
Doctor Albert G. Miller of San Mateo has now assumed his duties as new President of the California Medical Association. Working with Doctor Miller is the new President-Elect for CMA, Doctor Ralph W. Burnett of Bakersfield.

Doctor Miller, new leader of the more than 24,000 member physicians who make up the California Medical Association, has been involved in CMA activities for over 20 years.

A proctologist in the private practice of medi-



ALBERT G. MILLER, M.D.



RALPH W. BURNETT, M.D.

cine, Doctor Miller is a Fellow of the American College of Surgeons, and a graduate of the Stanford University School of Medicine.

He has been a member of the CMA House of Delegates since 1962. After being a CMA Councilor for four years, Doctor Miller was elected Chairman of the Council in 1967. He has been President of San Mateo County Medical Society, and is a Past President of the San Mateo County Surgical Society. He is also active in many civic, as well as medical association activities.

President-Elect Burnett, a general practitioner, was President of Kern County Medical Society in 1956. He was a trustee of the Foundation for Medical Care of Kern County for seven years and also served as its president. In 1963, Doctor Burnett was elected to the Blue Shield Board of Trustees.

Doctor Burnett has been active on the CMA Council for four years, and at present is Chairman of the CMA Committee on Insurance and Prepayment. He has also served as a member on the CMA Committee on Committees and the Commission on Medical Services.

Other CMA officers elected at the CMA's annual session in Los Angeles were: Speaker of the House of Delegates William F. Quinn, and Vice Speaker Joseph F. Boyle, both of Los Angeles, and both re-elected.

Newly elected Councilors are Nicholas P. Krikes of San Bernardino, Second District; and Arthur F. Howard of Fresno, Sixth District. Councilors Elmer F. Gooel, Joseph P. O'Connor, Harold Kay, and Albert G. Clark were re-elected to their positions.

Elected as new members to the AMA Delegation were Dudley M. Cobb, Jr., and Emmet L. Rixford. Alternate Delegates elected were Thomas N. Elmendorf, John V. Pollack, Herbert A. Holden, Ralph W. Schaffarzick, Frank A. Rogers, and Russell Fisher.

DRUG REACTIONS

"[Sir William] Osler said that man differs from other animals in his propensity for taking drugs. Perhaps man has survived, at least as an ambulatory patient, because he has a built-in defense, which is to forget to take the doses we [as physicians] prescribe. In hospitals, unfortunately, this kind of defense is breached; and everybody is after the man to take the drugs on time. We often find, though — even so — it's not 100 percent effective. But we certainly could make it easier for epidemiologists [studying adverse reactions to drugs], and incidentally for patients too, if we first of all prescribed fewer drugs per patient (I think ten drugs per patient is a pretty indefensible number as an average); and second if we were on the lookout for minor symptoms which could be premonitory of more severe symptoms. So then at least the next time the patient is scheduled to receive a drug, some warning might have been received, the patient might not be given that drug and an untoward result might be averted. The third thing is that all of us, I think, can improve the recording of moderate to major drug reactions in hospitals."

—ALBERT I. MENDELOFF, M.D., Baltimore
Extracted from *Audio-Digest General Practice,* Vol. 16, No. 45, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

Council Highlights

Highlights of the Actions of the California Medical Association Council Meetings, March 14 to 19, Los Angeles

This summary is published so that CMA membership may be advised in brief of the action of the Association's Council. It covers only major actions and is not intended as a detailed report. Full minutes of these meetings are available upon any member's request to the CMA office.

551st Meeting, March 14 to 19, 1969, Los Angeles

An ad hoc committee to study abortion laws in California was approved. The committee will make an in-depth study of a resolution discussed by the CMA House of Delegates at its meeting. The resolution urges CMA to recommend to the Legislature that it abolish all statutes and criminal laws dealing with abortion.

Expansion of duties of the Medical Staff Survey Committee was approved. The committee will make surveys of extended care facilities in general and public-owned hospitals.

A study on the future relationship of the hospital pharmacist and other paramedical personnel in relation to the physician was approved. It will be made by the CMA Scientific Board and the CMA Commission on Allied Health Professions.

A definition of "Nursing Home Care" was approved. It reads as follows:

"Patients whose medical conditions should properly be cared for in nursing homes are those with illnesses or disabilities which require continuing observation by qualified nursing personnel and periodic evaluation by physicians.

"Such illnesses or disabilities usually would be long-term in nature. They would be relatively stable in course and would require limited diagnostic procedures and application of treatment methods not ordinarily found in a patient's residence. Although restorative measures might be of benefit to patients receiving nursing home care, rehabilitation would not be the prime consideration of the general medical and nursing care plan carried out in nursing homes since it is more properly the function of other facilities."

Support of efforts to return Medi-Cal consultants to the county—and stop a shift of consultants from county to state direction—was approved.

Creation of a Task Force on Allied Health Professions was approved. The task force study will include the following: (1) executive order on reorganization of the Department of Professional and Vocational Standards; (2) proposal from the Board of Medical Examiners to establish an Allied Health Board. The task force will report to the Council no later than October.

A proposed regulation by the Department of Health Care Services to require physician participation by agreement—in order that a doctor be a provider—in Medi-Cal was opposed.

An amendment to the Medical Practice Act was approved. The amendment allows students to receive stipends for work done on a preceptorship basis.

The CMA Industry-Medical Committee was authorized to proceed with negotiations with the interim goals of a limited raise in Workmen's Compensation fees, and the ultimate goal of "usual and customary."

552nd Meeting, March 19, 1969, Los Angeles

The Council elected its officers, made its administrative appointments, reviewed and made committee appointments, and passed bank resolutions.

ALBERT G. MILLER, M.D. . . . . President
RALPH W. BURNETT, M.D., Bakersfield . . . President-Elect
WILLIAM F. QUINN, M.D. . . . . Speaker
JOSEPH F. BOYLE, M.D. . . . . Vice-Speaker
RICHARD S. WILBUR, M.D. . . . Chairman of the Council
HAROLD KAY, M.D. . . . . Vice-Chairman of the Council
HELEN B. WEYRAUCH, M.D. . . . . Secretary
MALCOLM S. M. WATTS, M.D. . . . . Editor
ROBERT L. THOMAS . . . . Executive Director
General Office, 693 Sutter St., San Francisco 94102 • 415 776-9400
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RICHARD W. LEMOS . . . . Sacramento Office
1127 11th St., Sacramento 95814 • 916 444-5532

In Memoriam

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

Benteen, Frederick Harry, Berkeley. Died 28 February 1969 in Kensington of coronary occlusion with myocardial infarction, aged 63. Graduate of University of California Medical School, Berkeley-San Francisco, 1931. Licensed in California in 1931. Doctor Benteen was a member of the Alameda-Contra Costa Medical Association.

⁂

Blank, Edward Arthur, Stockton. Died 6 January 1969 in Stockton of heart disease, aged 61 years. Graduate of Boston University School of Medicine, 1933. Licensed in California in 1957. Doctor Blank was a member of the San Joaquin County Medical Society.

⁂

Brainerd, Henry Dean, San Francisco. Died 18 March 1969, in San Francisco, aged 54. Graduate of University of California Medical School, Berkeley-San Francisco, 1939. Licensed in California in 1939. Doctor Brainerd was a member of the San Francisco Medical Society.

⁂

Camp, John Dexter, Los Angeles. Died 5 March 1969 in Los Angeles of cancer, aged 70. Graduate of Boston University School of Medicine, 1921. Licensed in California in 1951. Doctor Camp was a member of the Los Angeles County Medical Association.

⁂

Cuthbert, Esther Williams, Los Angeles. Died 18 March 1969 in Los Angeles of malignant lymphoma, aged 73. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1930. Licensed in California in 1930. M.D. degree from California College of Medicine, 1962. Doctor Cuthbert was a member of the Los Angeles County Medical Association.

⁂

Daniels, S. Richard, Montebello. Died 24 March 1969 in Demming, New Mexico, of coronary artery disease, aged 56. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1940. Licensed in California in 1940. M.D. degree from California College of Medicine, 1962. Doctor Daniels was a member of the Los Angeles County Medical Association.

⁂

Howell, William L., San Diego. Died 31 March 1969 in San Diego, aged 80. Graduate of Cornell University Medical College, New York, 1910. Licensed in California in 1942. Doctor Howell was a retired member of the San Diego County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

⁂

Kellogg, Frederick, Long Beach. Died 5 March 1969 in Long Beach of myocardial insufficiency, aged 62. Graduate of Harvard Medical School, Boston, 1931. Licensed in California in 1932. Doctor Kellogg was a member of the Los Angeles County Medical Association.

⁂

La France, Charles T., Riverside. Died 24 February 1969 in an airplane crash in South Formosa, aged 74. Graduate of College of Medical Evangelists, Loma Linda-Los Angeles, 1938. Licensed in California in 1938. Doctor La France was a member of the Los Angeles County Medical Association.

⁂

Lohse, John L., Oakland. Died 25 March 1969 in Oakland of acute pneumonitis, aged 92. Graduate of Oakland College of Medicine & Surgery, 1906. Licensed in California in 1906. Doctor Lohse was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

⁂

McColl, William F., Sr., San Diego. Died 8 March 1969 in San Diego, aged 73. Graduate of University of Buffalo School of Medicine, Buffalo, New York, 1921. Licensed in California in 1923. Doctor McColl was a retired member of the San Diego County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

⁂

McCullough, C. P., Riverside. Died 5 November 1968 of carcinoma of the lung, aged 80. Graduate of Rush Medical College, Chicago, 1914. Licensed in California in 1945. Doctor McCullough was a retired member of the Riverside County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

⁂

McDermott, Alza M., North Hollywood. Died 17 March 1969 in Los Angeles of heart disease, aged 68. Graduate of The Creighton University School of Medicine, Omaha, 1928. Licensed in California in 1939. Doctor McDermott was a member of the Los Angeles County Medical Association.

⁂

Michaels, Michael Wasylycia, Lancaster. Died 2 March 1969 in Loma Linda of acute myocardial infarction, aged 55. Graduate of College of Medical Evangelists, Loma Linda-Los Angeles, 1951. Licensed in California in 1952. Doctor Michaels was a member of the Los Angeles County Medical Association.

Miller, Ned David, Los Angeles. Died 20 March 1969 in Culver City of cardiac arrest, aged 82. Graduate of Jefferson Medical College of Philadelphia, 1916. Licensed in California in 1924. Doctor Miller was a member of the Los Angeles County Medical Association.

⁘

Northrup, Leila Warren, Los Angeles. Died 24 February 1969 in Santa Monica of cancer, aged 76. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1947. Licensed in California in 1947. M.D. degree from California College of Medicine, 1962. Doctor Northrup was a member of the Los Angeles County Medical Association.

⁘

Pettler, Samuel H., Los Angeles. Died 1 April 1969 in San Gabriel, aged 79. Graduate of Hahnemann Medical College of the Pacific, San Francisco, 1912. Licensed in California in 1912. Doctor Pettler was a member of the Los Angeles County Medical Association.

⁘

Reische, Alverda Elva, Berkeley. Died 11 March 1969 in Oakland of pulmonary edema due to myocardial insufficiency, aged 84. Graduate of University of California Medical School, Berkeley-San Francisco, 1920. Licensed in California in 1920. Doctor Reische was a member of the Alameda-Contra Costa Medical Association.

Sheldon, Elroy F., Los Angeles. Died 5 March 1969 in Los Angeles of cerebral hemorrhage, aged 72. Graduate of Harvard Medical School, Boston, 1928. Licensed in California in 1929. Doctor Sheldon was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

⁘

Turner, George R., San Diego. Died 25 March 1969 in Guelph, Ontario, Canada, aged 60. Graduate of University of Toronto Faculty of Medicine, 1936. Licensed in California in 1940. Doctor Turner was a member of the San Diego County Medical Society.

⁘

Veazey, Paul M., Santa Barbara. Died 6 April 1969 in Santa Barbara of brain tumor, aged 39. Graduate of Western Reserve School of Medicine, Cleveland, 1955. Licensed in California in 1964. Doctor Veazey was a member of the Santa Barbara County Medical Society.

⁘

Wilson, Llewellyn Edwards, Anaheim. Died 15 March 1969 in Anaheim, aged 68. Graduate of University of California Medical School, Berkeley-San Francisco, 1934. Licensed in California in 1934. Doctor Wilson was a member of the Orange County Medical Association.

PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H. Director, State Department of Public Health

Pollution in Paradise

CALIFORNIA HAS BECOME a state of first magnitude since the turn of the century when it was a quiet haven for would-be lotus-eaters. Today it ranks first among the 50 states in population, agriculture, industry and probably in the production of liquid, gaseous and solid wastes.

Solid wastes pile up at an average rate of 20 pounds a day for each Californian. That's more than 70 million pounds a year—70 million pounds of garbage, tree trimmings, lawn and street sweepings, broken glass, old bed springs, tin cans, fractured furniture, outworn appliances, junked automobiles, field crop residues, dead livestock, animal viscera, putrid leftovers from food processing, poisoned chemical and industrial wastes, steel mill slag, sewer sludge, and logging slash and brush—just to name a few pollutants.

What to do with all this rubbish?

Liquid, solid, and gaseous wastes may be disposed of in only three media—air, water and soil. Solid waste is unique as the only one which can directly affect all three. Burned, it is transformed to gaseous and particulate waste and contributes to air pollution. Disposed into or near the ocean, bays and streams, it can cause water pollution. Littered in open dumps, it creates unsightly land pollution.

And it is in just such ways that disposal is carried out in many localities. There is an all too prevalent tendency to dispose of the waste at the least cost and in a manner which barely satisfies minimum requirements for health and safety. Thus, many jurisdictions burn their waste in open dumps, or toss it over the fences of neighboring communities.

But man's environment is a complex ecosystem. Interfere with one aspect, and we disturb the whole system. Filling the tidelands and marshlands of the San Francisco Bay is not only objectionable from the esthetic and conservational points of view, it disturbs the ecology of the Bay's marine life, its water, tidal currents and flushing action, and it even alters the area's climate.

Aren't there state laws to govern the disposal of solid wastes? Yes, a few special purpose ones, but they are not comprehensive and they are not specifically designed to protect the health and well-being of our people.

Refuse disposal is an environmental health problem. The most serious health factor is domestic flies, vectors of disease. Flies propagate in enormous numbers in organic wastes, contaminate themselves in fecal material and may eventually contaminate man. Then there are rats, cockroaches and mosquitoes, as well as the threat of plague, a disease which is enzootic in certain of California's sylvatic rodent populations. Finally, unsightly and malodorous waste scattered over the countryside disturbs the psychological and esthetic well-being of the people, desecrating the landscape and degrading the very quality of life.

Fragmented authority, lack of cooperation, inadequate planning, low standards, poor financing and want of technologic means prevent any easy solution to the mounting problem of waste disposal.

California's State Health Department is the chief state agency involved. Grant funds provided by the Federal Government for a three-year California Solid Waste Study are making it possible to conduct a research project using systems analysis methods to unravel complexities and find solutions. An interim report, Volume I, *Status of Solid Waste Management,* was issued in September 1968.[1] Another extensive study of solid waste management in the entire state will be issued later this year. The report will become the basis of a department-recommended solid waste management program to be carried out at local levels.

The department defines solid waste management as a "planned system of effectively controlling the production, storage, collection, transportation, processing, and disposal or utilization of solid wastes in a sanitary, esthetically acceptable and economic manner."[2]

This is the objective of the department's program and it can be achieved.

REFERENCES

1. Department of Public Health, State of California: Status of Solid Waste Management in California (California Solid Waste Planning Study, Volume 1, Interim Report), Sept. 1968. Supported in part by U. S. Public Health Service Planning Grant (No. SO-2-UI-0008).

2. Ibid., II-1.

EPIDEMIC TEEN-AGE PREGNANCIES

"Consider the 120,000 out-of-wedlock babies born every year to American teen-agers. What does this tell us as parents? It tells us that at any given time, more than two percent of all high school age girls are pregnant. It also tells us that one girl in every six in this country will have an illegitimate pregnancy between her thirteenth and nineteenth birthdays.

"Every parent and anyone else who is interested in community health or community medicine must be asking himself two questions: why this epidemic of adolescent pregnancies and what can be done to prevent them? I do not have the answer to either question; but I have given both some thought.

"Society is playing a game of pretend about sex; but the child or young person caught up in this game does not have the wisdom to make valid value judgments. Situational ethics . . . is considered the best approach by many prominent psychologists; and many prominent churchmen now feel the same way. They are no longer shaking their fingers when boys and girls give in to natural biological urges and experiment a bit. They don't say, 'Stop, you're wrong.' They ask, 'Is it meaningful?' In this so-called 'new' morality, we are telling young people that nothing of itself can always be labelled wrong. . . . But there is one basic flaw in this new morality as it applies to teen-agers or for that matter as it applies to anyone; and that is, if you live by this code, you must accept the responsibility for your actions. This the teen-ager is incapable of doing."

—ROBERT A. SACK, M.D., Los Angeles
Extracted from *Audio-Digest Pediatrics,* Vol. 14, No. 23, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

EDUCATION NOTICES

Meetings and Courses

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of the dates of continuing education programs and the meetings of various medical organizations in California is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102; or phone: (415) 776-9400, extension 241.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Postgraduate Course Information

CMA:	**California Medical Association** For information contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. (415) 776-9400, ext. 241.
LLU:	**Loma Linda University** For information contact: John E. Peterson, M.D., Associate Dean for Research Affairs, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.
PMC:	**Pacific Medical Center** For information contact: Arthur Selzer, M.D., Chairman, Education Committee, Pacific Medical Center, Clay and Webster Streets, San Francisco 94115. (415) 931-8000.
STAN:	**Stanford University** For information contact: Thomas A. Gonda, M.D., Associate Dean, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5940.
UCD:	**University of California, Davis** For information contact: Charles J. Tupper, M.D., Dean, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0333.
UCI:	**University of California — California College of Medicine, Irvine** For information contact: Robert Combs, M.D., Associate Dean, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.
UCLA:	**University of California, Los Angeles** For information contact: Donald Brayton, M.D., Associate Dean and Head, Continuing Education in Medicine and the Health Sciences, 15-39 Rehabilitation Center, UCLA Center for the Health Sciences, Los Angeles 90024. (213) 825-6514.
UCSD:	**University of California, San Diego** For information contact: Clifford Grobstein, Ph.D., Dean, University of California, San Diego, School of Medicine, La Jolla 92038. (714) 453-2000.
UCSF:	**University of California, San Francisco** For information contact: Seymour M. Farber. M.D., Dean, Educational Services and Director, Continuing Education, Health Sciences, University of California Medical Center, San Francisco 94122. (415) 666-1692.
USC:	**University of Southern California** For information contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 225-1511, ext. 203.

MEDICINE

June 5-6—**Selected Subjects in Electrocardiography.** UCSF at Mt. Zion Hospital and Medical Center. Thursday-Friday. $55.

June 6 — **Allergy-Immunology Symposium.** STAN at Children's Convalescent Hospital. Friday. Contact: M. H. Jennison, M.D., Stanford's Convalescent Hospital, 520 Willow Rd., Palo Alto 94304.

June 7—**Neurology Symposium-Neurological Complications of Alcoholism.** Southern California Permanente Medical Group and Kaiser Foundation Hospitals at Statler-Hilton Hotel, Los Angeles. Saturday. Contact: Shirley Gach, Symposium Coordinator, Room 6014, 4900 Sunset Blvd., Los Angeles 90027.

June 9-11—**American Neurological Association.** Beverly Hilton Hotel, Los Angeles. Monday-Wednesday. Contact: Samuel Trufant, M.D., Cincinnati General Hospital, Cincinnati 45229.

August 17-20—**Advanced Seminars in Internal Medicine.** UCLA at Lake Arrowhead. Sunday-Wednesday.

August 26-Sept. 1—**Pacific Dermatological Association.** Princess Kalulana Hotel, Honolulu. Tuesday-Monday. Contact: John M. Shaw, M.D., Sec.-Treas., 419 South L Street, Tacoma, Wash. 98405.

September 9-10—**19th Annual Professional Symposium on Cardiovascular Diseases.** San Diego County Heart Association in cooperation with USC at Hilton Inn, San Diego. Contact: James E. Lasry, M.D., Symposium Chairman, 3330 - 3rd Avenue, San Diego 92103.

September 14-20—**American Electroencephalographic Society.** El Cortez Hotel, San Diego. Sunday-Saturday. Contact: Philip T. White, M.D., 8700 W. Wisconsin Ave., Milwaukee 53226.

October 1-3 — **Annual Postgraduate Symposium on Heart Disease.** St. Francis Hotel, San Francisco. Wednesday-Friday. Contact: Gene C. Taylor, Executive Director, 259 Geary Street, San Francisco 94102.

October 10-12 — **Scientific Program, California Society of Internal Medicine.** Coronado. Friday-Sunday. Contact: Cynthia Bell, Exec. Sec., 350 Post Street, San Francisco 94108.

Grand Rounds

Tuesdays

Medical Grand Rounds: UCLA. 9-10:30 a.m., Assembly Hall, Harbor General Hospital, Torrance.

Wednesdays

Grand Rounds in Internal Medicine: UCSF. 10:30-12:00 noon.

USC Department of Medicine Grand Rounds. 11:00 a.m., Room 1645, Los Angeles County-USC Medical Center.

UCI Grand Rounds in Medicine. 12:30 p.m., Auditorium, School of Nursing, Orange County Medical Center.

Grand Rounds in Internal Medicine. 1:30-3:00 p.m., Fresno General Hospital.

Thursdays

Medical Grand Rounds, UCLA. 10:30-12:00 noon, Room C3-105, UCLA Medical Center.

Fridays

Medical Grand Rounds—CRMP Area IV. 8:00 a.m., Courtroom, Third Floor, Kern County General Hospital, Bakersfield.

Medical Grand Rounds—CRMP Area IV. 8:30 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

Infectious Disease Grand Rounds—USC. 10:00 a.m., Auditorium, Children's Division Building, Los Angeles County-USC Medical Center, Los Angeles.

Medical Grand Rounds—CRMP Area IV. 1st and 3rd Fridays, 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles.

Medical Grand Rounds—CRMP Area IV. 2-3:00 p.m., Classroom, Third Floor, Fresno General Hospital, Fresno.

Rheumatology Grand Rounds — USC, 11:30 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles.

OBSTETRICS AND GYNECOLOGY

August 13-17—**Second Annual UCLA Advanced Seminars in Obstetrics and Gynecology.** UCLA at Lake Arrowhead. Wednesday-Sunday.

PEDIATRICS

June 20-21—**Postgraduate Seminar: Pediatrics.** Children's Hospital of Orange County, Orange. Friday-Saturday. $30. Contact: Merl J. Carson, M.D., Medical Director, Children's Hospital of Orange County, 1109 West La Veta Avenue, Orange. (714) 538-8831.

June 25-27—**Tenth Annual Pediatric Seminar.** Children's Hospital, San Diego at Hanalei Hotel, San Diego. Wednesday-Friday. Contact: H. Wayne Cleeton, Assistant Administrator, Children's Hospital, 8001 Frost Street, San Diego 92123.

July 11-12—**Pediatric Allergy.** PMC. Friday-Saturday.

August 13-17 — **Advanced Seminars in Pediatrics.** UCLA at Lake Arrowhead. Wednesday-Sunday.

September 27-28—**Pediatric Neurology.** UCLA. Saturday-Sunday.

Grand Rounds

Tuesdays

UCLA. 8:30-9:30 a.m., Sixth Floor Conference Room, Harbor General Hospital, Torrance.

USC. 8:30 a.m., Auditorium, Children's Division Building, Los Angeles County-USC Medical Center, Los Angeles.

CRMP Area IV. 8:30 a.m., Conference Room, Sixth Floor, Harbor General Hospital, Torrance.

CRMP Area IV. 8:30 a.m., Room 4-A, Kern County General Hospital, Bakersfield.

Wednesdays

UCI. 8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and the Auditorium, Children's Hospital of Orange County.

Thursdays

UCSF. 8:30-10:00 a.m., Room 664, Science Building, UCSF.

Cedars of Lebanon Hospital. 8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

Fridays

CRMP Area IV. 8:00 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA.

PSYCHIATRY

June 18—**My Third Year of Residency Training with Professor Carstairs.** Agnews State Hospital, San Jose. Wednesday. Contact: J. Elizabeth Jeffress, M.D., Director of Professional Education, Agnews State Hospital, San Jose 95114.

October 28-Nov. 2—**12th Annual Scientific Meeting and Workshop.** American Society of Clinical Hypnosis. Jack Tar Hotel, San Francisco. Tuesday-Sunday. Contact: F. D. Nowlin, Exec. Sec., 800 Washington Ave., S.E., Minneapolis 55414.

PATHOLOGY-RADIOLOGY

June 10-14—**Electrophoresis Workshop.** UCSF at Children's Hospital. Tuesday-Saturday.

SURGERY

June 2-5—**Southwestern Surgical Congress.** Sahara Tahoe Hotel, Lake Tahoe. Monday-Thursday. Contact: Jack A. Barney, M.D., 301 Pasteur Bldg., Oklahoma City 73103.

June 5-7—**Highlights of Ophthalmology.** PMC. Thursday-Saturday.

June 11-13—**Fractures.** USC. Wednesday-Friday.

June 13-15—**Ethics and Organ Transplants.** USC at Vacation Village Hotel, Mission Bay, San Diego, Friday-Sunday.

June 23-25—**Postgraduate Course in Ophthalmology.** Stanford University. Monday-Wednesday. $100. Contact: Division of Ophthalmology, Stanford University School of Medicine, Stanford 94305.

June 28-29—**Nasal Reconstruction.** UCLA. Saturday-Sunday.

July 24-26—**Strabismus Conference.** PMC. Thursday-Saturday.

August 1-3—**Instrumentation and Monitoring During Anesthesia.** UCLA. Friday-Sunday.

August 21-23—**Retinal Detachment Conference.** PMC. Thursday-Saturday. $125.

September 8—**Orthopedic Symposium-Spine Mechanics.** Southern California Permanente Medical Group and Kaiser Foundation Hospitals at Statler-Hilton Hotel, Los Angeles. Monday, 2-5:30 p.m. Contact: Shirley Gach, Symposium Coordinator, Rm. 6014, 4900 Sunset Blvd., Los Angeles 90027.

October 6-10—**Annual Meeting, American College of Surgeons.** Fairmont Hotel, San Francisco. Monday-Friday. Contact: John Paul North, M.D., 55 E. Erie Street, Chicago 60611.

October 14-22—**Pan-Pacific Surgical Association.** Hawaiian Hilton, Honolulu. Tuesday-Wednesday. Contact: Mrs. Harriet N. DeVault, Exec. Sec., Rm. 236, Alexander Young Bldg., Honolulu 96813.

October 25-29—**American Society of Anesthesiologists.** Hilton Hotel, San Francisco. Saturday-Wednesday. Contact: John W. Andes, Exec. Sec., 515 Busse Highway, Park Ridge, Ill. 60068.

Grand Rounds

Wednesdays

CRMP Area IV. 7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield.

CRMP Area IV. 1st and 3rd Wednesdays. 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles.

Fridays

UCI. 1-2:00 p.m., Auditorium, Orange County Medical Center, Orange.

Saturdays

CRMP Area IV. 9:00 a.m., Room 73-105, Health Sciences Center, UCLA.

CRMP Area IV. 8:30 a.m., Assembly Room, Harbor General Hospital, Torrance.

OF INTEREST TO ALL PHYSICIANS

June 4-5—**Sports Medicine—Football.** USC at Los Angeles Hilton Hotel. Wednesday-Thursday.

June 5-7—**Sacramento Valley Counties Regional Postgraduate Institute—Three Faces of Medical Practice: Drugs and Drug Reactions, Cancer of the Alimentary Tract, Selected Aspects of Trauma—Current Concepts of Professional Liability.** California Medical Association in cooperation with UCSF and Sacramento Valley Counties Medical Societies. Sahara Tahoe Hotel, Lake Tahoe. Thursday-Saturday. $20. Contact: CMA.

June 7—**Office Management.** UCLA at St. Joseph's Hospital, Burbank. Saturday.

June 19-21—**American Medical Women's Association.** Alta Mira Hotel, Sausalito. Thursday-Saturday. Contact: Mrs. Gertrude F. Conroy, 1740 Broadway, New York 10019.

June 14-15—**Sex Disorders in Clinical Practice.** UCSF. Saturday-Sunday. $25.

June 23-26—**Annual Meeting, Western Branch, American Public Health Association.** Jack London Square, Oakland. Monday-Thursday. Contact: Joseph Weinstein, President, 655 Sutter Street, San Francisco 94102.

July 2-6—**Seminars for General Practitioners.** UCLA at Lake Arrowhead. Wednesday-Sunday.

July 14-18—**Hospital Information Systems: Techniques and Applications.** USC School of Engineering. Contact: W. D. Campbell, Coordinator, Noncredit Programs, USC.

August 11—**National Medical Association.** Hilton Hotel, San Francisco. Contact: John T. Givens, M.D., Exec-Sec., 2400 Corprew Avenue, Norfolk 23504.

August 16-27—**12th Annual Postgraduate Refresher Course.** USC at Honolulu and Maui, Hawaii. Saturday-Wednesday.

October 11-12—**Kern Postgraduate Conference.** Kern County General Hospital at Civic Auditorium, Bakersfield. Saturday-Sunday. Contact: George A. Paulsen, M.D., Conference Committee Chairman, 2603 G St., Bakersfield 93301.

October 17-18—**Western Industrial Medical Association.** Jack Tar Hotel, San Francisco. Friday-Saturday. Contact: Mr. B. H. Bravinder, 2180 Milvia St., Berkeley 94704.

CONTINUOUSLY

Basic Home Course in Electrocardiography. One year postgraduate series, ECG interpretation by mail. Physicians may register at any time. $100 (52 issues). Contact: USC.

Audio-Digest Foundation. A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: General Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Anesthesiology. Ophthalmology. Catalog of lectures and panel discussions in all areas of medical practice also available. Contact: Mr. Claron L. Oakley, Editor, 619 S. Westlake Ave., Los Angeles 90057.

RADIO AND TELEVISION

Medical Radio Conferences. Live from UCSF. Tuesdays, 12:30-1:30. Heard on:

Auburn—KAFI-FM (101.1 mc)
Berkeley—KPFA-B-FM (94.1 mc)
Bishop—KIBS-FM (100.7 mc)
Chico—KEWT-FM (93.7 mc)
Eureka—KRED (1480 kc)
Fresno—KXQR-FM (102.7 mc)
King City—KRKC (1490 kc)
Los Banos—KLBS-FM (95.9 mc)
Mendocino—KMFB-FM (92.7 mc)
Salinas—KRSA-FM (100.7 mc)
Santa Maria—KSMA-FM (102.5 mc)
Stockton—KSTN-FM (107.3 mc)
Susanville—KSUE (1240 kc)
Tulare—KBOS-FM (95 mc)

June 3—**Problems of Drug Abuse.**

June 10—**Controversies of Breast Cancer.**

September, broadcasting resumes.

California
Medicine

Intestinal Bacteria

The Role They Play in Normal Physiology, Pathologic Physiology, and Infection

SYDNEY M. FINEGOLD, M.D., *Los Angeles*

■ *Anaerobic bacteria predominate in the normal human fecal flora, outnumbering aerobes at least 100 to one. The two most prevalent organisms are* Bacteroides fragilis *and* Bifidobacterium. *Ileostomy flora is, on the other hand, chiefly aerobic and the total count is lower (10^8 per ml of fluid, compared to 10^{10} per gram for feces). In normal people, small bowel bacterial counts are generally 10^5 per ml or less. The upper small bowel consists primarily of Gram-positive aerobes in small numbers. In the terminal ileum, counts are higher and aerobes and anaerobes are present in equal numbers. In the presence of acute obstruction and certain bowel stasis or other syndromes, the small bowel flora may become relatively profuse and fecal in type. The stomach normally has less than 10^3 organisms per ml but counts are higher in gastric samples with pH above 4.0.*

Intestinal bacteria are important in such processes as conversion of bilirubin to urobilinogen, supply of vitamin K to the host, defense against infection, bile acid deconjugation and conversion, infections related to the bowel, the malabsorption of blind loop and other bacterial overgrowth syndromes, and hepatic coma.

IT IS LIKELY that we are accounting for only 10 to 25 percent of the normal intestinal bacterial flora by the best of techniques currently being used systematically. Until recent years, most bacteriologic studies of bowel flora used only aerobic incubation, and the few studies which included anaerobic technique were quite inadequate. Indeed, most studies of the anaerobic intestinal flora are still inadequate. Limited studies utilizing the excellent anaerobic techniques developed by Hungate and modified by Moore have revealed the presence of organisms in human feces previously thought to be present only in ruminants—*Methanobacterium*[1] and *Butyrivibrio*.[2] Choice of media may also influence results significantly. Certain

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Submitted 29 January 1969.

Reprint requests to: Infectious Disease Section, Veterans Administration Center, Sawtelle and Wilshire Boulevards, Los Angeles 90073.

organisms have specific growth requirements; for example, some strains of *Bacteroides melaninogenicus* require menadione or similar compounds. The use of a battery of media, including selective and differential media, not only simplifies bacteriological analysis but may lead to greater recovery of certain organisms. Incubation at room temperature may be necessary to recover the intestinal pathogen, *Yersinia enterocolitica,* but is not known to be necessary for any normal component of the intestinal tract.

Enteric Bacteria in Normal Adults

The normal human fecal flora of adults is predominantly anaerobic, aerobes accounting for only 0.1 to 1.0 percent of the cultivable flora.[3] The anaerobe which is most prevalent and probably invariably present normally is *Bacteroides fragilis;* the average count of this species is 10^{10} to 10^{11} per gram of wet feces. Other Gram-negative anaerobic bacilli are found less frequently. *Sphaerophorus* is found in over half of humans studied, with a mean count of 10^9 per gram when present. *B. melaninogenicus* is present in somewhat fewer than half the population and is found in small numbers (10^4 per gram). Fusiform bacilli are found only occasionally, but counts may be relatively high. *Bacteroides oralis* is probably not part of the resident flora of the bowel.

The second most prevalent organism is *Bifidobacterium,* a Gram-positive, non-sporulating anaerobic bacillus also known by such names as *Lactobacillus bifidus* and *Actinomyces bifidus.* It is found in two-thirds of fecal samples, with average counts of 10^9 per gram.

Other Gram-positive non-sporeforming anaerobic bacilli belonging to the tribe *Lactobacilleae* are found in similar numbers in at least one-third of people. The classification of these organisms may be very difficult; most belong to the genera *Eubacterium* and *Ramibacterium.* The more aerotolerant members of this tribe belong to the genus *Lactobacillus* and are really aerobic or microaerophilic. These organisms are found in 50 percent of people, with mean counts (when present) of 10^7 per gram.

Other anaerobes, found in feces of over one-third of people, include *Clostridium* and anaerobic cocci of various types—both showing counts of 10^8 per gram when present.

The major elements of the aerobic fecal flora are coliforms and streptococci. *Escherichia coli* is the predominant coliform, present in virtually all people in a count of 10^7 per gram of feces. Enterococci of various types, chiefly *Streptococcus faecalis,* are found in similar numbers in most people. Streptococci of the viridans type are found less frequently.

The flora of ileostomy effluent, by contrast, is chiefly aerobic and the overall count is lower (10^8 per ml, compared with 10^{10} grams for feces.[4,5] Mean counts of coliforms, aerobic streptococci and *Lactobacillus* are similar in ileostomy effluent and feces, but enterococci are found in a smaller percentage of ileostomy patients. Staphylococci or micrococci and yeast *(Candida)* are found in moderate numbers ($10^{5\text{-}6}$ per ml) in about half of ileostomy patients. *B. fragilis* was absent from ileostomy effluent of all five patients studied in our laboratory, but several other anaerobes were found (each in one patient only); the mean count of anaerobes was $<10^6$ per ml.

In normal persons, the small bowel flora is relatively simple and large numbers of organisms are not found.[6,7] Total counts are generally 10^5 or less per ml, except for the distal ileum, where counts usually are about 10^6 per ml. The flora increases in number and type as one progresses from the duodenum to the ileum. The upper small bowel consists primarily of Gram-positive aerobes, with no *Bacteroides* and rare anaerobes of other types. In the terminal ileum, there are approximately equal numbers of aerobes and anaerobes; here, coliforms are the most prevalent aerobes and *Bacteroides* and bifid bacilli the most common anaerobes. Gram-positive cocci and rods, similar to organisms found in the intestinal juice, have been found in small numbers associated with the mucous layer of small intestinal biopsy specimens.[8] In the presence of acute obstruction of the small intestine, the small bowel flora may become relatively profuse and fecal in type.[9]

The stomach normally has very small numbers ($<10^3$ per ml) of viridans streptococci, lactobacilli and fungi.[6,10] Counts tend to be distinctly higher in gastric samples which have higher pH, particularly above 4.0.[10]

Role of Normal Intestinal Bacteria

There is much to be learned concerning the role the normal intestinal flora plays in various physiologic processes of man. Conversion of bilirubin to urobilinogens takes place in the intestine through the activity of the intestinal flora. This conversion may be decreased by administration of chlortetracycline (and undoubtedly by other antibiotics as well), but the component(s) of the flora responsible for the changes are unknown. The vitamin K needs of the host are supplied by intestinal bacteria; both coliforms and *Bacteroides* are known to be sources of this vitamin, but since *Bacteroides fragilis* normally is present to the extent of 100 to 1,000 times that of *E. coli* the anaerobe is much more important in this regard.[11] The decrease of serum cholesterol and the "intermediate" pool of cholesterol resulting from administration of oral neomycin[12] is probably not a result of changes in the intestinal flora.

The gut flora is undoubtedly important to the host in other aspects of nutrition but studies in man, in particular, are very inadequate. For additional information, the excellent review by Donaldson[13] should be read.

The intestinal microflora may be an important component of our defense against infection but this has not been adequately studied in man. Mice are rendered much more susceptible to experimental *Salmonella* infection after treatment with oral streptomycin reduces the *Bacteroides* count in the colonic flora.[14] On the other hand, *Endamoeba histolytica* cannot infect the germfree guinea pig unless one of several aerobic bacteria is also present.

Conjugated bile acids are split by the action of the normal large bowel flora[15]; usually only free bile acids are found in the feces.[16] Although enterococci are very active in this deconjugation process, the anaerobes *B. fragilis, Sphaerophorus,* and *Bifidobacterium* are also very active and are much more prevalent in the colonic flora.[17] Although it had been thought that bile acids were absorbed or reabsorbed from the lower small intestine, recent work indicates that there is significant absorption of bile acids from the human large bowel.[18] Cholic acid is converted to deoxycholic acid in the colon and both of these free bile acids are absorbed well from this site.[16,18] Various Gram-positive nonsporulating anaerobes are known to be effective in this conversion[19]; the Gram-negative anaerobes have not been studied adequately.

Enteric Bacteria and Infection

Knowledge of the normal bowel flora is also important in proper management of a variety of infections in which they may become involved—such infections as appendiceal abscess, peritonitis, subphrenic and subhepatic abscess, pyogenic liver abscess, pylephlebitis, diverticulitis, peri-rectal abscess, and postoperative infections following surgical operations on the bowel or elsewhere in the abdomen.[20-22] Gram-negative anaerobic bacilli, anaerobic cocci and, to a lesser extent, coliforms, enterococci and clostridia play very important roles in such infections. The Gram-positive non-sporeforming rods are distinctly less pathogenic and lactobacilli are virtually non-pathogenic.

Disturbances of the normal flora secondary to administration of antibacterial compounds may lead to several types of problems, most poorly defined and inadequately studied. Thus, overwhelming and fatal enteric infection or endotoxemia or both have been reported in guinea pigs and hamsters receiving penicillin G, erythromycin, tetracycline, or lincomycin.[23] The most commonly recognized enteric complication in man has been staphylococcal enterocolitis,[24] reported after use of a variety of antibiotics ineffective against staphylococci. Less well established is the possibility of *Salmonella* enteritis following antibiotic therapy.[25] It is likely that other pathogens may also be implicated in antibiotic-induced diarrhea. Still less well investigated is the prospect that changes in normal flora may account for diarrhea.[26]

There is also evidence to indicate that the intestinal flora may be involved in protection from systemic infection and the effects of endotoxin.[27] Preoperative bowel preparation with antibiotics before operation for cancerous lesions may predispose to subsequent recurrence of the cancer at the suture line.[28]

Enteric Bacteria in Non-Infective Diseases

It is also known that bowel flora, normal and abnormal (sometimes abnormal only in location and numbers), plays a very important part in certain pathophysiologic states but, again, our knowledge of these processes and the organisms involved is still fragmentary.

Overgrowth of bacteria in the small bowel is responsible for the malabsorption seen in such conditions as blind loop syndrome, intestinal stricture, gastrocolic fistula, enteroenterostomy, diverticula, and poorly functioning gastrojejunostomy.[13] It is less well established, but similar bacterial overgrowth is very likely responsible for the malabsorption which may be seen in intestinal scleroderma[29] and diabetic neuropathy[30] and which will respond to therapy with agents such as tetracycline. It may also be involved in some cases of sprue-like illness in patients with dysgammaglobulinemia[15]; the diarrhea in some of these patients responds to tetracycline. The steatorrhea seen in these syndromes is thought to be due to bacterial deconjugation of bile acids in the upper small intestine where these acids are normally found in the conjugated form. Conjugated bile acids are necessary for normal micelle formation, in turn necessary for normal fat absorption. The relative abilities of various bacteria to deconjugate bile acids has already been noted. For this and other reasons (foul odor of upper intestinal contents in some cases, ineffectiveness of neomycin, and effectiveness of both tetracycline and lincomycin in bacterial overgrowth syndromes), it is reasonable to feel that anaerobes play a crucial role in the majority of patients with this type of malabsorption.[31] The mechanism of vitamin B_{12} malabsorption is less well understood, but many feel it is due to bacterial binding of the vitamin.

Increased activity of intestinal bacteria in patients with malabsorption is also reflected in increased urinary excretion of bacterial metabolites of tryptophan such as indoleacetic acid.[13] Elevated urinary levels of indican and indoleacetic acid may also be seen in patients with Hartnup disease due to poor intestinal absorption of tryptophan and bacterial action on this compound. Bacterial conversion of dibasic amino acids poorly absorbed from the intestine may be responsible for high excretion of heterocyclic amines in patients with cystinuria.

The facts that patients with tropical sprue respond to antibacterial agents[32] and that antibacterial agents administered prophylactically (in a controlled study) were moderately effective in preventing diarrhea in tourists[33] indicate the likelihood that intestinal bacteria play significant roles in these situations as well. To date, there has been little direct support for this; eventually, appropriate techniques should establish the role of bacteria in these diseases.

Whipple's disease is more likely a specific infection than a syndrome resulting from derangement of normal bowel flora. Although tetracycline therapy is effective, there is much disagreement as to the specific identity of the bacillary bodies seen in the gut on electron microscopy.

Finally, hepatic coma is recognized as a state in which bacterial activity in the bowel contributes significantly to the clinical manifestations. Oral neomycin or kanamycin have been used extensively for prevention and treatment of this condition, but other drugs such as chlortetracycline are known to be effective. Bacterial production of ammonia from nitrogenous substrates is one of the basic problems in this syndrome. The studies of Martini and coworkers[34] demonstrated that, although normal persons had a negligible bacterial flora in the small bowel, cirrhotic patients had many coliforms and enterococci in the ileum and some had these organisms in the jejunum and duodenum as well. Other important factors that may contribute to hepatic coma are inability of the liver to detoxify, and absorption from the gut of ammonium that has by-passed the liver through portal collateral vessels.

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COLOVESICAL FISTULA FROM DIVERTICULITIS

"In our series of 17 patients with colovesical fistula from diverticulitis, the 100 percent symptoms—symptoms found in all of the patients—included pneumaturia and gross pyuria. The 50 percent symptoms were fever, feces in the urine, and urinary cystitis symptoms; and way down the line were hematuria and melena.

"The history was far and away the most helpful and most important aid in diagnosis. I think that perhaps in this day and age we don't pay enough attention to the history. We tried to figure out how long the patients had had the process going on before a fistula became overt; and it was about two years. So I think in a patient with diverticulitis with symptoms of bladder irritation, perhaps we might consider this possibility a little earlier. Cystoscopy ordinarily is just suggestive. It's confirmatory; but you don't just look in and see a nice big hole that you can put a catheter in or something of that sort. Urography was quite helpful in a number of cases."

—Harry M. Spence, M.D., Dallas

Extracted from *Audio-Digest Surgery,* Vol. 15, No. 22, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

Internal Neurolysis in Treatment

BARTON A. BROWN, M.D., *San Francisco*

■ *Many peripheral nerve injuries are of a contusing type with resultant intraneural scarring which causes neurologic deficit even though the nerve is still in continuity. Internal neurolysis can relieve pain and restore neurologic function in such lesions. It is important that such lesions be recognized early, fully evaluated and carefully followed so that surgical intervention can be carried out before permanent changes can develop in the denervated muscles, joints and skin. The procedure is frequently rewarded with prompt and gratifying results. The risk is minimal and the patient need spend only a short time in hospital.*

INTERNAL NEUROLYSIS—the lysing of intraneural scar tissue with microsurgical technique—is often useful for restoration of function in peripheral nerves that are deteriorating following injury. Prompt use of the operation is important, lest wasting changes become irreversible with delay, yet the procedure is not universally known because the care of peripheral nerve injuries is scattered amongst general practitioners, orthopedic surgeons, plastic surgeons, general surgeons, hand surgeons and neurosurgeons. Even many neurosurgeons are unaware of the value of internal neurolysis and indications for it.

Intraneural scarring of the kind for which this treatment is useful is produced by acute contusion of a peripheral nerve with subsequent edema, hemorrhage and fibrosis, or by chronic irritation such as frequently occurs in an ulnar nerve when there is a valgus deformity of the elbow. Since the axons in a peripheral nerve are surrounded by multiple layers of connective tissue, the end result of blunt trauma which does not sever the nerve or axons is dense scarring in the connective tissue surrounding the axons. This produces a physiologic obstruction to nerve conduction. It is this obstruction that can be relieved by internal neurolysis.

The procedure is of value mainly in situations in which the nerve is in continuity but is malfunctioning after acute or chronic trauma. The malfunction may stem from tardy ulnar palsy secondary to an old elbow injury, or it may be caused by a direct blow over the nerve, or by cast or tourniquet pressure, or by surgical or injection injury. The clinical course may be characterized by acute and complete loss of function, or by partial loss or by slow progressive impairment.

When a patient with such a lesion is seen, a complete evaluation should be made of the motor and sensory function in the distribution of the affected nerve. Then six weeks is allowed to elapse from the time of injury to see if spontaneous improvement will occur. If improvement is not evident by then, as determined either by clinical or electromyographic examination, exploration of the nerve and internal neurolysis are indicated. Spontaneous improvement can of course come about in some cases after longer periods than the six-week wait recommended here, but the risks of the procedure are minimal and the risk of delay becomes progressively greater. Longer delay must take into account that such changes as muscle atrophy and fibrosis, interstitial edema, joint stiffening and fibrosis, motor end-plate atrophy and skin deterioration are progressing in the denervated segment and can reach the point of irreversibility.

Submitted, revised, 26 March 1969.
Reprint requests to: 2000 Van Ness Avenue, San Francisco 94109.

umatic Peripheral Nerve Lesions

Electromyographic and nerve conduction studies are valuable adjuncts to evaluation both before and after operation.

Reports of Cases

The following cases are illustrative.

Case 1. A 27-year-old man sustained multiple injuries in July 1963, among them severe contusion of the left elbow which caused numbness in the ulnar distribution and moderate weakness. The other injuries healed, but he noted progressive weakness of grip in the left hand and intensification of the numbness. When first examined neurologically in March 1964, the small muscles of the affected hand were estimated at only 20 to 25 percent of normal strength. There was moderate sensory loss appropriate to the ulnar distribution, and Tinel's sign was evoked at the elbow. On exploration of the left ulnar nerve in April 1964, considerable extrinsic cicatrization and severe intrinsic damage were noted. Internal neurolysis was carried out. The nerve was not transplanted. Ten days later, sensation and motor function in the ulnar area were improved. After a year, only minimal atrophy could be detected in the small muscles of the hand. Strength of grip was 80 to 90 percent of normal. Only very mild sensory changes could be detected in the ulnar area.

Case 2. A 36-year-old woman, a clerk at a check-out counter in a market, had drooping of the right shoulder and aching in that region following excision of a posterior cervical lymph node on that side. Numbness in the right occipital region also developed.

Pronounced atrophy and weakness of the superior portion of the right trapezius were noted on examination. The scapula was rotated, presenting itself as a bony prominence in the trapezoid ridge. There was winging in the superior part of the scapula. The patient could not control the position of the scapula for shoulder motions. Sternomastoid function was normal. A diagnosis of distal eleventh cranial nerve palsy was made. On surgical exploration at the site of the lymph node excision, the eleventh cranial nerve was found to be matted in considerable scar tissue. The external scar was dissected free and internal neurolysis was done. There was no immediate change following the procedure but within three months improvement could be detected and in nine months the patient was able to resume work full time at her former job. Bulk and strength returned sufficiently in the trapezius to permit scapular fixation. The estimated return of strength was to approximately 60 percent. Pain had disappeared.

Case 3. A 40-year-old man was injured in November 1965 when a heavy piece of machinery compressed the lateral aspect of the left arm above the elbow. There was immediate and complete motor and sensory loss in the radial distribution. When the patient was examined neurologically one month after the accident, there was good function in the triceps but no radial nerve function distal to the lesion. At operation the radial nerve in the lateral aspect of the arm was found to be smaller than normal and some intrinsic scarring was noted. Response to nerve stimulation was good distal to the lesion and absent proximal to it.

Internal neurolysis was carried out and immediately afterward there was evidence of distal muscular contraction on stimulation of the nerve proximal to the lesion. Within three days after the procedure the patient began to have muscular contractions in the brachioradialis, and over the next few months he regained function in all muscle groups supplied by the radial nerve. By July 1966, no specific weakness could be detected, and hypalgesia in the radial distribution was minimal.

Case 4. A 3-year-old girl was neurologically examined four months after onset of foot-drop in the right lower extremity that occurred following an injection of penicillin in the right buttocks. The child was wearing a foot-drop support and there had been no improvement. On examination the girth of the right calf was observed to be 3 cm less than the right, and there was no function of any anterior compartment musculature. Moderate weakness of the gastrocnemius and hypesthesia of the great toe and dorsal foot were noted. The right ankle jerk was less than normal. The diagnosis was sciatic neuropathy with primary involvement of the peroneal division.

At operation the sciatic nerve was exposed at the sciatic notch and mild external adhesions were found. There was also decided intrinsic scarring of the nerve, particularly in the peroneal portion, and internal neurolysis was carried out. Two days later the first activity was noted in the anterior compartment of the leg. Within a month the patient was able to resist pressure with the anterior tibial and peronei. Nine months after operation the difference in size between the two calves was only 5 mm and motor function was felt to be normal.

Case 5. A 36-year-old woman had satisfactory bony union after a compound fracture and dislocation of the left ankle but an extremely sensitive area posterior to the medial malleolus remained two years later. Any tapping or pressure there produced painful paresthesias in the medial three toes and there was, in addition, constant low-grade pain in this region.

On surgical exploration of the tibial nerve, dense scarring was observed around and in the nerve, for which internal and external neurolysis was done. The chronic pain abated soon after operation, and over a longer period the sensitivity of the nerve to external pressure diminished.

In the five cases presented, internal neurolysis relieved pain or dysfunction that might not have been abated had not the reason been diagnosed and the procedure undertaken before irreversible deterioration could take place.

CHARACTERISTICS OF GLIOMA OF THE OPTIC NERVE

"Glioma of the optic nerve may be quite characteristic in its clinical appearance as well as in its x-ray appearance. The textbooks say that a glioma will push the eye *down* and *in*; but this isn't true because, as you know, if the optic nerve is splinted and straightened out and becomes stiff, there is only one way to push the eye and that would be *out* and possibly *down*. This is characteristic of advanced glioma of the optic nerve."

—Joseph A. C. Wadsworth, M.D., Durham, N.C.
Extracted from *Audio-Digest Ophthalmology,* Vol. 6, No. 24, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

Cervical Cancer

Use of a Non-Physician Health Team for Screening Procedures

PURVIS L. MARTIN, M.D., *San Diego*

■ *A team of non-physician personnel has been trained in cytologic screening for cervical cancer. In a county hospital clinic setting among low income women whose annual pelvic examinations were being bypassed by physicians, this three-person team has performed pelvic examinations and screening under physician supervision for one year.*

Results of the first year's experience, measured in cancer detection and in recognition and referral of benign gynecological disease as well, would suggest that a non-physician team, with a registered nurse doing a pelvic examination of screening type, can screen for cervical cancer and other pelvic disease efficiently and without a significant lowering of the quality of medical care.

The training and use of teams of allied health care personnel directed by physicians is suggested as a practical means of overcoming the increasing shortage of physician services in annual screening for cervical cancer among low income women.

MEDICAL CONTROL OF CERVICAL CANCER by annual cytologic screening continues to lag far behind its potential. It is generally agreed that if every adult female in a given population were to have annual examination of a Papanicolaou smear, most cases of cervical cancer would be detected and safely eliminated before reaching invasive stages. Yet today, 25 years after Papanicolaou and Traut[1] proved the value of vaginal cytology in cervical cancer control, less than half of American women receive the protection of annual smear examination. Lower income women, well known to be relatively high in cervical cancer risk, are receiving generally even less cytologic protection than higher income women who are accustomed to seeing physicians for regular check-up examinations. In less affluent nations of the world, the percentage of women who are being cytologically screened drops to almost zero. Even with combined community efforts, no large population has ever been completely screened.

The customary procedure of a physician's pelvic examination and cytologic smear provides satis-

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Sponsored by United States Public Health Service, Grant #05033-A67, P. L. Martin, M.D.

Submitted 2 January 1969.

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factory and efficient protection for the individual, but apparently there are simply not enough physicians with the time and the interest to screen all adult women of this country each year, much less all women of the world. Preventable deaths continue to occur. Clearly, there is a need to explore any possible additional method which could help to fill in the thin spots in annual cytologic screening of total populations.

The objective of this pilot project is to test the value and the efficiency of a team of paramedical personnel who have been trained in case-finding, public education, screening pelvic examinations, and cytologic scanning for cervical cancer. This team has been placed in a clinic setting of low income women who were being passed over cytologically by the routine physician medical services of a large county-university hospital. For the past year, working independently, but under close medical supervision, this team has attempted to perform a screening pelvic examination with cytologic smear and scanning on all women coming to this institution, who would otherwise have had no pelvic examination at all.

Material and Background

Probably the most complete mass population screening effort yet to be reported is the ten-year San Diego County Medical Society Uterine Cancer Control Project.[2] Our population sampling survey in 1966 showed that 82 percent of the total female population above age 21 in this county of more than one million people had received at least one cytologic examination.[3] Yet this left 18 percent who had never been examined cytologically. And 41 percent had not had a smear examination each year. Furthermore, the preponderance of women who were being missed in this community screening effort were those in the low income high risk group. Many of them were accustomed to seeking medical care, when they felt they needed it, in the large free or part-pay clinics of the San Diego County Hospital. Here, repeated efforts to establish routine annual pelvic examination with smears on all adult female patients had failed. Only the clinics in gynecology and in obstetrics succeeded in obtaining routine annual smears. In clinics where the medical focus was outside the female pelvis, such as orthopedics, eye, and even medicine, the case load was too great, the patient attitude too resistant or apathetic, and the customary physician's pelvic examination too time-consuming and unwieldy to make it an annual routine for all patients. This provided as a test population a fairly well delineated population of low income women in the San Diego community, currently unscreened, with medical facilities available for examination, supervision and medical referral.

During the development of this project, the San Diego County Hospital was placed under the direction of the University of California. Now named University Hospital of San Diego County, this institution became the major clinical facility for the new University of California, San Diego School of Medicine. With a U.S.P.H.S. supporting grant, this project was sponsored by the Department of Obstetrics and Gynecology and co-sponsored by the Department of Pathology.

The Non-Physician Health Team

Our team includes three paramedical personnel, selected and trained to function as a unit in areas where regular physician services are spread too thin to expect routine annual pelvic and cytologic examination on all women:

(1) **An Administrative Assistant** with a background as a medical secretary. This team leader is responsible for case-finding, coordinating team activities, record-keeping and reporting, correspondence and supplies.

(2) **A Registered Nurse** with a background of experience in office nursing with a group of gynecologists. This registered nurse is responsible for performing a screening type of pelvic examination with a cervical smear on all adult female patients who are found not to have had a smear within a year, and who would otherwise not have any pelvic examination during the course of their medical visit.

(3) **A Cytotechnician**, previously trained as a scanner in a pathologist's office. This cytotechnician stains and scans all project slides for cytologic abnormality. All abnormal findings are referred to the Department of Pathology for checking and disposition.

Intra-Hospital Project Relationships

Problems in establishing this project into the operational structure of a large general hospital were of course anticipated. The performance of even a limited physical examination by a registered nurse was a new concept to many, and eyebrows were raised in a number of clinical departments.

Planning conferences with the hospital administrator resulted in his approval of the project and his wholehearted cooperation. Directives from the administrator to all departments, including housekeeping, purchasing, records and engineering, explained the purpose of the project and gave it "official status." The director of nurses issued separate instructions to all floor nurses and all clinic nurses, orienting all hospital nursing in the purpose of the project and assuring nursing cooperation. The attending staff was briefed on the project in staff meetings, followed by question and answer staff discussions. The intern and resident staff in all clinical departments was fully briefed and has been helpful and cooperative. Spurred by concern that a nurse might discover a cancer that a physician had missed (as indeed she has), interns and residents were quick to reduce the number of patients that were slipping by without pelvic examination.

Project Procedure

Each morning before outpatient clinic hours, the project nurse and the project administrative assistant check inpatient charts on the various hospital wards, searching for patients who are to be discharged without having had a pelvic examination and smear. The project nurse carries with her a small bag containing speculae, gloves, lubricant, applicators, Ayre spatulas, slides and fixative. After a brief explanation, each unscreened patient receives a screening pelvic examination in bed, including speculum examination and Ayre scraping of the cervix.

In the clinic a small examining room is assigned for the project examinations. Charts of patients who have clinic appointments are checked each morning in each clinic, and a flag is put on any that do not show that the patient has had a cytologic smear within a year. When the patient has completed her medical visit, if a pelvic examination and smear have not been recorded, she is invited to the nearby project room "for a cancer smear." First, the nurse calls her attention to public education displays and brochures in the room. The nurse then takes a brief and pertinent history, fills out our project card, and individually reinforces patient knowledge in cancer detection and the "cancer smear." At the same time, on a regular gynecologic examining table, with minimum draping and maximum assurance, she quickly performs a bimanual pelvic examination for gross benign disease or tumors. Following this, she inserts a speculum, snaps a 35 mm photograph of the cervix, and obtains a wooden Ayre spatula scraping from the portio and a specimen from the cervical canal by cotton applicator twist. Slides are spray-fixed and sent to the pathology laboratory for staining and scanning. As the patient leaves, she is again told the importance of returning each year for a repeat smear. The nurse refers all patients with suspicious symptoms or abnormal pelvic findings to the gynecology clinic for physician evaluation. She scrupulously avoids giving advice that could be construed as medical treatment, explaining to the patient her position as a nurse and not a physician.

TABLE 1.—*Cancer Detection by Paramedical Personnel Team*

Total patients screened	1412
Suspicious or positive smears	14 (1.0%)
Cancer by tissue diagnosis	6 (0.4%)
1 early invasive, cervix	
1 adenocarcinoma, endometrium	
4 pre-invasive, cervix	
Dysplasia	3
Chronic cervicitis	5

In the laboratory the project cytotechnician stains and scans all slides. All abnormal or atypical findings are referred to the project pathologist who, using the five classifications of Papanicolaou, reports his findings. Reports are sent to project headquarters in the Department of Obstetrics and Gynecology. Class I reports are placed in an automatic "tickler" file for recall of the patient in one year. Class II reports are placed in a six-month recall file. For all Class III, IV or V reports, the patient is recalled to the gynecology clinic for a physician's examination, diagnostic study and appropriate treatment.

Results

Cancer Detection

Results in cancer detection are given in Table 1. Fourteen patients of 1,412 screened were found to have suspicious or positive smears. Tissue diagnosis confirmed unsuspected cancer, all by-passed by the usual physician services in this hospital, in six patients. This yield of one cancer per 250 patients, or 0.4 percent, is approximately the same cancer yield that was reported in physician screening in the early days of the San Diego County Medical Society project.[4]

Other Disease

One hundred forty-one additional patients were

TABLE 2.—*Disease Other than Uterus Cancer Detected through Examination by Team of Paramedical Personnel*

Patients receiving screening pelvic examination		1412
Patients referred for physician care		141 (10%)
Carcinoma of rectum	1	
Prolapse and procidentia	5	
Fibroids	15	
Cystocoele and/or rectocoele	25	
Adnexal mass	15	
Cervical polyps	9	
Bartholin cysts	5	
Hormonal evaluation	26	
Inguinal hernia	1	
Other symptoms and conditions	39	
Patients receiving gynecologic operation		25
Major	12	
Minor	13	

found on the nurse's screening pelvic examination to have significant abnormalities and were referred to the gynecology outpatient clinic for physician evaluation. The yield in benign and other pelvic pathologic findings is given in Table 2. This project was started at just about the time the full effect of Title 19 Federal Legislation in this hospital suddenly reduced the number of gynecologic operative patients to about half its former level. Our paramedical screening clinic led many patients, who otherwise would have been by-passed, to needed surgical care. Twenty-five patients referred from the project received gynecological operations for benign disease at this hospital.

In one Negro patient the project nurse noted that the cervix and vaginal mucosa were startlingly white against the black background of her skin. On physician referral hemoglobin was found to be less than 5 grams per 100 ml, which in turn led to the finding of an operable carcinoma of the rectum.

Color Photography of the Cervix

A 35 mm color photograph of the cervix is taken with a Coreco Clinical Camera during each screening pelvic examination. Photographs are scanned by the chief resident in gynecology. In the early months of the project, photography was felt to provide closer physician supervision and a double check on what the nurse was seeing and what she might be missing. As her experience increased, our confidence in her ability to recognize and refer the abnormal also increased. Photography has provided us with a wealth of photographs of the cervix, but little additional clinical help.

Validity of the "Screening Pelvic Examination"

In order to test diagnostic skill and accuracy of our project nurse in the screening pelvic examination, a series of 25 of her examinations was checked by the chief resident in gynecology. Findings of the nurse and of the resident were recorded separately on cards which were then handed to the project director for comparing. No significant gynecologic lesions or pathologic changes were reported by the resident and missed by the nurse. Indeed, findings recorded separately by the two examiners were remarkably consistent.

Public Education and Patient Acceptance

A cheerful, friendly and persuasive attitude, a natural attribute of our project nurse, have created an almost perfect record of patient acceptance of pelvic examination for the project. She takes full advantage of her unique opportunity to overcome apathy and ignorance in the patients she sees. With physician coaching she has developed a patient teaching program that combines lay education in cancer detection with good medical public relations.

Discussion

As the need for physician services draws further and further ahead of the rate at which physicians can be educated, medical health teams composed of non-physician personnel, directed by physicians, may well help to fill in thin spots in medical care. In the earlier days of cytological practice, it became obvious that physicians alone could not adequately scan all the slides that needed to be scanned. Technicians were trained to become full-time professionals in scanning. Gradually cytotechnologists became as adept and even more efficient than many hurried physicians who simply had not enough time to spend on scanning. Now, since the entire female half of the world's adult population needs a pelvic and cytologic examination each year, and since there are not enough physicians to perform these examinations, additional means must be devised to get the job done. Observations from this pilot project would suggest that non-physician personnel can be trained successfullly in cervical cancer screening, and further, that non-physician pelvic cytologic screening can be done without basically reducing the quality of medical care. Results of non-physician screening, measured in terms of cancer detections, were approximately equal to the results of physician screening.

Our team has started its second year of operation, with additional procedures in cancer screening. Breast examinations and public education in self-examination for breast cancer have been added to the routine screening pelvic examination which the project nurse performs on each patient. The second year's experience will be reported when it has been completed.

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IS THE TUBE *FUNCTIONING,* OR JUST OPEN?

"How do we go about evaluating the Eustachian tube? There are many tests that will tell whether or not the tube is patent, but this is entirely different from telling whether or not it will respond to normal physiologic demands. This is, I find, the hardest concept to get across. For some reason, people feel that if you can politzerize a tube, the tubal function is normal. This test doesn't tell you anything about tubal function. Lack of ability to politzerize a tube would certainly indicate a significant obstruction; but ability to politzerize it tells you absolutely nothing about whether the tube is [functioning] or would function under duress.

"One method I've found useful for evaluating the Eustachian tube is putting three or four drops of ophthalmic sulfisoxazole (Gantrisin) solution in the ear and then seeing how long it takes for the patient to taste it. This is a relatively handy test for people who are not allergic to sulfonamides. You can use it to determine how effectively the tube opens. But this hinges, of course, on whether the patient can taste Gantrisin. Some people can notice its bitter taste and some can't; if they don't, you have to put some on the tongue to see if they could have tasted it had it gone in. . . . It goes without saying that there has to be a perforated ear drum or a myringotomy so that we are really communicating with the middle ear."

—JAMES A. DONALDSON, M.D., Seattle

Extracted from *Audio-Digest Otorhinolaryngology,* Vol. 1, No. 8, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

Mediastinoscopy

A Valuable Diagnostic Aid

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R. L. GOODE, M.D., *Stanford*

■ *Mediastinoscopy is a safe and simple endoscopic procedure for the exploration of the superior mediastinum. It provides useful information as to the possible resectability of bronchogenic carcinoma, or for establishing the diagnosis of primary tumors of the mediastinum, metastatic disease and a variety of chronic granulomata.*

MEDIASTINOSCOPY IS AN EFFECTIVE AND SAFE procedure for palpation, direct inspection or biopsy of lesions in the superior mediastinum. The yield of positive tissue diagnosis is much higher than with scalene node biopsy and as an alternative to open thoracotomy it is far less traumatic. In spite of the advantages of mediastinoscopy over older surgical diagnostic methods, the technique is not widely used in North America. This paper will give reasons why it should be.

Harken and associates[1] described the lateral cervico-mediastinal exploration in 1954. Due to a high incidence of complications, the method they used was replaced by a more logical midline approach introduced in 1959 by Carlens.[2] Initially, mediastinoscopy was proposed as an extension of scalene node biopsy in order to determine the resectability of bronchogenic carcinoma. It was later found to be an effective diagnostic tool for other mediastinal masses, including chronic granulomatous disorders, metastatic tumors, cysts and lymphomas.

The evidence that mediastinoscopy provides a higher diagnostic yield has been demonstrated both in man and in experimental animals. Tegner[3] performed mediastinoscopy in 163 instances in which disease was present, and the diagnostic result was "positive" in 39 percent of cases of pulmonary carcinoma and in 98 percent of cases of pulmonary sarcoidosis. With use of scalene node biopsy in 311 cases the apposite figures fell to 19 percent and 64 percent, respectively. Johner[4] inoculated dogs intrabronchially with *Histoplasma capsulatum.* Several weeks later both scalene node biopsy and mediastinoscopy were performed. The former method yielded 27 percent positive results, whereas a 91 percent positive diagnostic rate was made by mediastinoscopy.

When mediastinal node biopsy is negative in a case of pulmonary carcinoma, the rate of resectability is approximately 90 percent.[5] This figure falls to 60 percent for negative scalene node biopsy. The positive yield of mediastinal node biopsy diminishes as the lesion moves peripherally. Reynders'[6] 300 cases illustrate this fact. In central lesions mediastinoscopy gave a 60 percent positive diagnosis; 50 percent positive when only atelectatic or poorly defined lesions were encountered; 10 percent for peripheral lesions, and 7 percent for coin lesions.

With present preoperative diagnostic methods, carcinoma of the lung is found to be unresectable in 35 to 40 percent of cases by the time operation is carried out. By using mediastinoscopy[5] this

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Submitted 10 January 1969.

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number can be lowered to about 10 percent, as shown in Table 1. A great number of patients with unresectable tumors, therefore, are spared the expense and morbidity of thoracotomy.

The usefulness of mediastinoscopy in the diagnosis of pulmonary sarcoidosis is shown in Table 2.

Indications

There are two main indications for mediastinoscopy:

1. Diagnosis of mediastinal and parahilar pulmonary masses without an exploratory thoracotomy.
2. Determination of resectability of pulmonary carcinoma.

Surgical Technique

The patient is placed supine with the neck extended. The upper thorax, chin, and neck are prepared and draped and 1 percent Xylocaine® with epinephrine is injected subcutaneously over the trachea and suprasternal notch. A 6 cm transverse skin incision is made approximately two fingerbreadths above the manubrium and dissection is carried down to the pre-tracheal fascia. It is important that the pre-tracheal fascia be divided because the plane for finger dissection lies between the trachea and the fascia. At this point, approximately 2 ml of 1 percent Xylocaine® solution is injected into the tracheal lumen to reduce the cough reflex. Blunt dissection, between the trachea and pre-tracheal fascia, is carried gently down along the anterior surface of the trachea into the mediastinum. It is extremely important that the surgeon be thoroughly familiar with the anatomical configuration of the mediastinum (Figure 1). Anteriorly, the innominate artery and the aortic arch can be readily palpated, as can the left common carotid artery. An assessment of the mediastinum can be made with the index finger as it passes downward; and should the patient complain during this procedure, a small amount of Xylocaine® may be placed into the field of dissection. Blunt dissection is continued until the tracheal bifurcation and right and left mainstem bronchi can be clearly palpated. Masses or nodes may be partially dissected free with gentle blunt dissection. This portion of the technique progresses with great ease unless fibrosis has developed there, as from previous irradiation or inflammation.

TABLE 1.—*Comparison of Diagnostic Value of Mediastinoscopy and Scalene Node Biopsy for Determination of Resectability of Bronchogenic Carcinoma*

Reported by	*Percent Resectable when Negative by* *Node Biopsy*	 *Mediastinoscopy*
Wilson[8]	55	—
Reynders[6]	60	90
Hosie[5]	60	90
Bergh[12]	—	80

TABLE 2.—*Diagnostic Value of Mediastinoscopy as Compared with Scalene Node Biopsy in Pulmonary Sarcoidosis*

Reported by	*Percent Yield for Positive Diagnosis by* *Scalene Node Biopsy*	 *Mediastinoscopy*
Reynders[6]	—	100
Carlens[9]	—	100
Skinner[10]	70	87
Tegner[3]	64	98

Following finger dissection, a mediastinoscope (Figure 2) is introduced into the pre-tracheal space and is passed inferiorly into the mediastinum. Two points must be kept in mind: The surgeon must see the tracheal rings, and he must never push the mediastinoscope into an undissected area. Further dissection is carried out either with the index finger or, under direct endoscopic vision, with a pair of long forceps carrying a small dissection sponge marked with a black silk suture, or with a specially designed spreader that accompanies the mediastinoscopy set. Should sharp dissection through fibrous bands be required, blunt-tipped laryngeal scissors may be used. Paratracheal, tracheal, bronchial, and subcarinal lymph nodes can all be readily reached and partially dissected in preparation for biopsy. Generally, many of the nodes encountered in the adult city dweller are stained with anthracotic pigment and are thus readily identified.

It is imperative that needle aspiration be employed if the operator is at all in doubt before a specimen for biopsy is excised from a mass. Non-fatal bleeding problems from nicking the superior vena cava, azygous vein and bronchial arteries have been reported in the literature. The other great veins which lie anterior to the arteries are not at risk. The right pulmonary artery is out of harm's way, as it lies anterior to the subcarinal nodes. However, the bronchial artery as it crosses in front of the left and right mainstem bronchi tends to pass through this mass of lymphoid tissue. The left recurrent laryngeal nerve is generally well away from the field of dissection between the

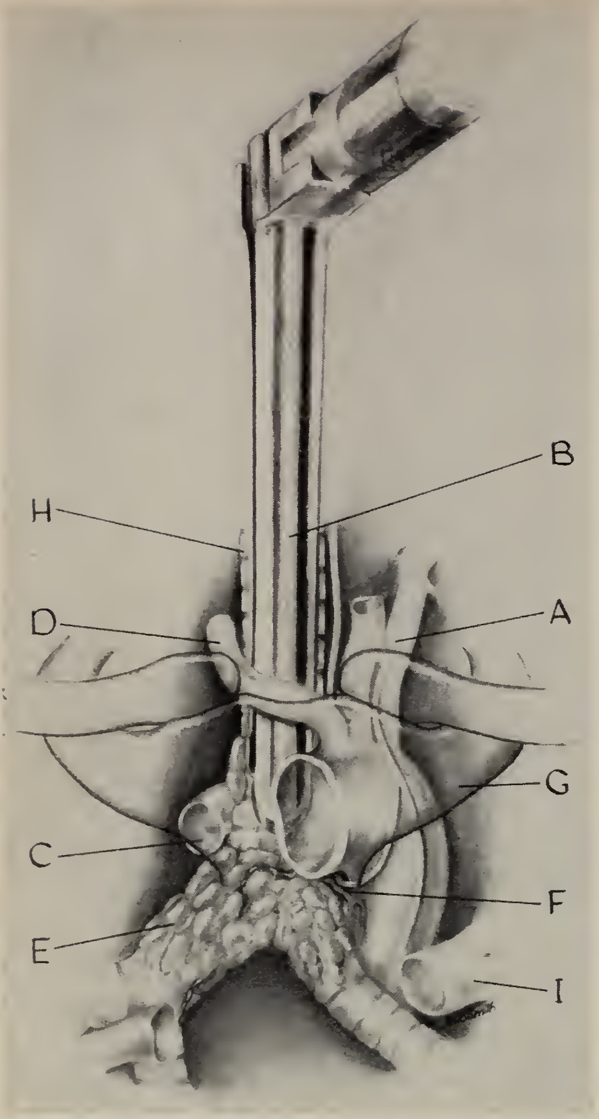

Figure 1.—Important anatomical structures in the upper mediastinum: A, Left recurrent laryngeal nerve. B, Mediastinoscope in place. C, Azygous vein. D, Innominate artery. E, Carinal lymph nodes. F, Bronchial artery. G, Left first rib. H, Trachea. I, Pulmonary artery.

esophagus and the trachea. If the node in question cannot be entirely dissected free, cup forceps may be used following aspiration identification. A slight ooze from the biopsy site is expected, but bleeding of any significant nature following excision of a specimen is rare and generally stops after brief compression. If bleeding is a problem, gelfoam may be packed over the bleeding site and pressure exerted for a period of minutes. The gelfoam packing may be left in place following completion of the procedure. Following removal of the mediastinoscope, the dissected space is obliterated by a collapse of the soft tissue, providing additional hemostasis. The wound is closed in layers and a small pressure dressing applied.

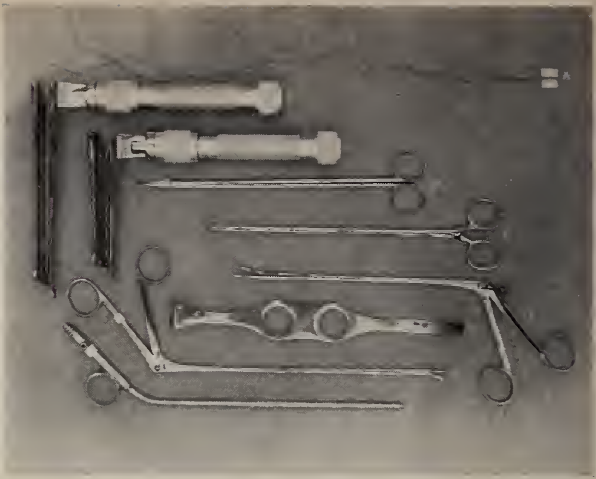

Figure 2.—Mediastinoscopy instruments: A, Cottonoid pledget. B, Long mediastinoscope. C, Short mediastinoscope. D, Scissors. E, Curved clamp. F, Blunt dissecting forceps. G, Retractor. H, Cupped biopsy forceps. I, Velveteye suction tip.

Despite the fact that general anesthesia has been exclusively employed by other investigators in order to keep the patients more comfortable, the patients we have operated upon under local anesthesia have not reported undue discomfort during the procedure and are ambulatory and on a full diet immediately following the operation. They are generally discharged the next day.

Ward and coworkers[13] expressed preference for local anesthesia, for bleeding was less, the hazard of general anesthesia was eliminated and the operating room time was shortened.

Complications

Mediastinoscopy is regarded as an unusually safe procedure. In a series of 1,087 cases analyzed and reported by Flynn,[11] the mortality rate was 0.3 percent (four cases), and the morbidity 2.6 percent (31 cases). In a series of 300 cases over a four-year period, Bergh and associates[12] noted the following complications: Two cases of pneumothorax; three cases of left recurrent laryngeal nerve paralysis, in one of which function returned completely over a one-year period; three cases of hemorrhage, all responding to packing; and two deaths within a two-week period following the procedure. It was felt, however, that mediastinoscopy was not the cause of death in either case. Other reports in the literature give a very low morbidity and mortality rate for this procedure, as compared with a reported mortality rate of 10 percent for thoracotomy.[6]

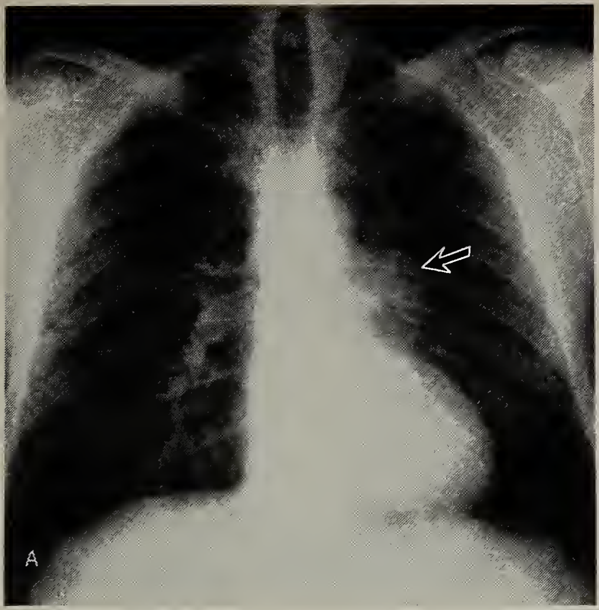

Figure 3 (Case 1).—X-ray film showing left hilar mass (arrow) which later was found to be metastatic carcinoma to an anthracotic parahilar lymph node.

Reports of Cases

Case 1. A 44-year-old white man was in good health until four weeks before admission to Stanford University Hospital in January, 1968, with a slowly enlarging lump on the right side of the forehead. This mass was excised and found to be anaplastic carcinoma. In a thorough examination, with emphasis on the gastrointestinal tract and thyroid gland, no significant abnormality was noted except for the presence of a very small left hilar mass (Figure 3).

Bronchoscopy and left scalene node biopsy were negative. Mediastinoscopy was performed under general anesthesia. Biopsy of an anthracotic carinal node revealed carcinoma. Later, a follow-up report from the referring physician indicated the primary lesion had been found in the colon.

Case 2. A 30-year-old male radiologist presented with self diagnosis of Hodgkin's disease made on the basis of bilateral hilar adenopathy on a routine x-ray film of the chest. Restrospective examination of previous chest films revealed no abnormalities a year earlier.

Other than anxiety engendered by his assumption that he had Hodgkin's disease, the patient was virtually asymptomatic. Physical examination was normal except for mild psoriasis. Laboratory tests and appropriate skin tests were negative. Mediastinoscopy was performed and biopsy of lymph nodes revealed sarcoidosis.

Case 3. A 24-year-old healthy white woman was admitted to Stanford University Hospital in June 1967 for the evaluation of a totally asymptomatic mediastinal mass discovered on a routine x-ray film of the chest. Physical examination was unremarkable, as were all laboratory studies save for a positive histoplasmin skin test.

Bronchoscopy and right scalene node biopsy were negative. In July 1967 mediastinoscopy was carried out. Microscopic evaluation of tissue removed from a firm mediastinal mass revealed a typical granulomatous process compatible with histoplasmosis. The patient was subsequently treated with amphotericin-B and when last observed was asymptomatic and the mediastinal mass as observed radiographically, was regressing.

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Use of LSD in the Haight-Ashbury

Observations at a Neighborhood Clinic

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■ *The philosophy of the Haight-Ashbury subculture is in great part dependent on the* LSD*-induced psychedelic experience. The Haight-Ashbury Medical Clinic in treating large numbers of patients having problems with abuse of* LSD *made observations on the* LSD *reaction and the types of* LSD *preparations being used among the youth of Haight-Ashbury. In addition descriptions of the acute and chronic psychological toxicity secondary to* LSD *are presented with recommendations for treatment and a discussion of the personality types involved. Finally the problems of potential neurotoxicity and chromosomal damage are presented.*

It is apparent that "Madison Avenue" techniques have produced a multiplicity of black market LSD *preparations. The use of impure* LSD *in improper environmental circumstances by inexperienced or prepsychotic adolescents has brought about a decided increase in the acute and chronic toxicity associated with this drug.*

SURVEILLANCE, EVALUATION AND TREATMENT of various drug problems is one of the primary functions of the Haight-Ashbury Medical Clinic. Of great interest to the general medical community has been the use and abuse of LSD (lysergic acid saure diethylamide). Physiologically the compound acts as a sympathomimetic agent: It mimics the effects that are brought about when the sympathetic nervous system is stimulated. After LSD is taken the pupils dilate, the blood pressure rises slightly, and the pulse quickens. The physiologic effects are quite minor, however, compared with the profound psychological effects that are seen.

Psychological or Behavioral Effects

A latent period of 35 to 45 minutes follows the ingestion of an average dose of LSD (150 to 200 mg). After the initial sympathetic response, a feeling of depersonalization and loss of body image is experienced. This early response in inexperienced users may cause great anxiety, and is probably the most common cause of an acute adverse reaction or "bad trip." The subject initially notices a change in his perception of environment, with objects changing shape and color. Illusions of this nature are the most common perceptual alterations.

Hallucinations (false sensory perceptions without a basis in external reality) are rather rare with LSD and when they do occur are more accurately described as pseudohallucinations in that the per-

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son usually does not lose critical self judgment during this experience.

Another rather remarkable perceptual change is synesthesia, the translation of one type of sensory experience into another. If one is listening to music, for example, he may "see" colored vibrations of the music coming from the record player, or he may "smell" purple.

There are much larger swings of mood in the LSD user than under the effects of "traditional" drugs; a more pronounced emotional lability, and a much greater suggestability. An early stage in the LSD experience may often be euphoric. If the individual is asked, "Why are you laughing?" the answer may be, "I don't know, really, but I just feel like laughing." The euphoria, however, can rapidly change to sadness brought about by very small changes in the environment. The sight of blue sky can generate ecstacy over its beautiful color. But if the sun goes behind a cloud, the subject's mood can quickly change to one of sadness and it seems that everything in the world is turning gray. Time orientation is frequently affected, also. Past, present and future frequently get mixed up.

Accepted, normal, even trivial phenomena, seen under the influence of LSD frequently assume dramatically increased or important new perspectives. For example, a person who has taken the drug may fix upon a red rose and develop a transient, but complicated philosophy of oneness with nature and God. This "ideational" alteration in philosophy may persist into the post-LSD period and is in great part responsible for the unifying philosophy of the newly evolved psychedelic subculture.

What a person experiences while under the influence of LSD depends greatly on his personal structure, his "set" or attitude before the experience, and the environment in which the drug experience is had. Variation in these factors can greatly alter the individual drug experience.

A subject under the influence of LSD usually exhibits inappropriate affect and symbolically altered speech patterns. The latter revolve around verbal concepts of visual distortions: for example, "Wow" is a word often used when it appears that all other descriptive words fail. Verbalizations common to the LSD experience are such expressions as: "White light; clear light; I can see; I can really see; I understand" (even when it appears to an observer that there is no change in the amount or kind of light, or that there is nothing cogent to see or understand).

LSD users often seem to themselves to be conversing on a high, philosophical level, although they may be making no apparent sense to the listener. Paranoia may be generated, exhibiting itself in fear of friends, police officers, and other real — or imagined — people who are "following" or "watching" the subject.

Different Forms of LSD "on the Street"

Referred to as "acid" on the streets, LSD has been greatly influenced by Madison Avenue techniques in its merchandising. Black market LSD manufacturers use special brand names, different shapes and colors, to differentiate their product from others. The proper treatment of an acute drug reaction depends in great part on an accurate history, and the array of exotic names can be confusing to a physician unaccustomed to treating cases of black market LSD ingestion. Many preparations containing LSD have appeared on the street with such esoteric names as "White Lightning," "Blue Dots," "Yellow Dots," "Purple Wedges," "Purple Flats," "Purple Owsleys," "Pink Dots," "Orange Wedges," "Green Caps," "Blue Caps," "Yellow Caps," "Brown Caps," "Paisley Caps" and "Pink Wedges."

Quality varies from one brand to another, both in the amount of LSD contained and the amount of contaminating ingredients, such as methamphetamine. A discrepancy also exists between the number of micrograms the dealers claim for their capsules or tablets and the amount they actually contain. The "street" dosage in micrograms (called "mics") is generally six to seven times larger than the actual clinical measurement. The "Blue Dots," for example, were claimed to contain about 900 to 1200 "mics" of LSD, but actually contained 150 to 200 clinical micrograms. A particular brand does not stay on the "street" very long in the Haight-Ashbury. Usually it is not manufactured in sufficient quantity to sustain a prolonged sales campaign. Also, when a particular brand has been accepted as "righteous" (or good) LSD, phoney copies are quickly brought out by the competition. The "Blue Dot," for example, was an aspirin tablet splashed with a blue dot on one side, probably applied with an eyedropper. After the "Blue Dot" had won consumer approval, tablets of Vitamin C or aspirin began to appear, dotted with blue food coloring or blue ink, instead of the original coloring which contained LSD.

Contamination of LSD with Methamphetamine

Methamphetamine crystals or "speed" (depending on the frame of reference) have appeared in great abundance in the Haight-Ashbury. Because of its small cost and ease of synthesis, it is often mixed with small quantities of LSD and sold as "pure acid." This mixture increases the likelihood of a "bad trip," mainly because of the intense sympathomimetic effects of the amphetamines. The tachycardia, muscle tremor and anxiety produced by "speed" are often magnified by the LSD-sensitized mind into a panic reaction. The reaction is often called a "death trip" by the user.

Psychological Toxicity

The adverse effects of LSD at present appear to be largely psychological in nature and can lead to several varieties of "bad trips." Susceptibility to "bad trips" is not absolutely dose-related, but depends upon the experience, maturity and personality of the user, as well as upon the external environment in which the trip is taking place.

The most common "bad trip" is the simple anxiety type of panic reaction. The inexperienced user is most susceptible to this reaction. The beginning changes or perceptions are often frightening, for they have little if any basis for comparison in everyday reality. A panic reaction in the more experienced user can often be credited to the high dosage he has taken.

The other kind of "bad trip" is toxic psychosis, commonly defined as a major break with reality secondary to an intoxicant. For example, the individual under the influence of LSD may have a frightening illusion of bodily distortion which suddenly seems real.

After taking the drug one can feel it has "gotten away" from him, that he no longer has control of the psychological effects he is experiencing. He wants to be taken out of this state immediately. He sometimes tries to flee the situation physically, or he may become quite paranoid and suspicious of other people, and lash out at them.

Some persons under LSD show decided changes in cognition or very poor judgment. They may have the feeling that they can really fly, and go out of windows. Some users have been reported walking into the sea, feeling they were "part of the universe." Some have described a feeling of immortality: "It doesn't matter if my body dies; my spirit will live." This mind-body dissociation leads to a variety of problems, including accidental "suicide."

Prolonged Psychotic Reactions

Although there is no evidence of organic brain damage with LSD use, there often appears to be serious long-term personality disruption, particularly in those who have had acute adverse reactions. These prolonged psychotic reactions may look like an endogenous paranoid schizophrenic reaction, and occur most often in persons with preexisting psychological problems.

Another adverse side effect is the recurrence of the acute reaction many days, and sometimes weeks, after the drug was taken. A patient with such a "flashback" becomes quite frightened; he feels he is losing his mind. The recurrence phenomenon is relatively rare, but it becomes more common with those who take the drug frequently or have had adverse reactions. We have also seen recurrent panic reactions, long-term depressions, and long-term perceptual alterations after an acute adverse LSD reaction.

Treatment

Treatment of the acute LSD reaction should be non-punitive and aimed at providing supportive care. If the user suspects "establishment" criticisms and senses that he is being used as a guinea pig (for example, in a situation where six to nine observers are in the room) he will fight any help offered. Conversing relaxedly can help the physician in his diagnosis and at the same time put the patient at ease. Quick movements should be avoided, as they may be misinterpreted. Make the patient comfortable (let him walk around, sit down, stand, lie down, or smoke if wishes to). However, *sometimes* the patient may become more agitated when he walks around, and the simple suggestion, "Why not sit down and relax," may help calm him.

It should be noted that the pattern of LSD use differs from the psychosis pattern familiar to most physicians. The LSD user is generally from the middle class, is probably well educated, and should be approached at that level.

Techniques for Treating The Acute Panic Reaction

The acute panic reaction, as stated earlier, can be divided into two types and there are two sepa-

Personality Types and Their Relationship to LSD Toxicity

The nature of adverse reactions to LSD can only be understood in relationship to the environment in which the drug is taken and the personality type of the person taking the drug.

The Haight-Ashbury subculture can be divided into four basic groups.

1. The core-committed hippie who had a particular consistent philosophical system and his two drugs that he used almost exclusively were marijuana (the social drug) and LSD (his religious agent). Whether he achieved this religious or psychotherapeutic effect we are not in a position to comment upon; but his stated motivation for the drug was to achieve a transcendental state of religious experience, or to achieve some goal in personal analysis.
2. The sociopathic element—which contained the Hell's Angels, the Gypsy Jokers, Negro militants, methamphetamine dealers, and criminals.
3. A prepsychotic element — the Haight-Ashbury in its acceptance of anyone who will come down there on their terms attracted a very large number of prepsychotic individuals that "could not make it" in regular society, and in fact oftentimes had a long record of institutionalization. These individuals were not particularly violent, but the particular group which can be called "the ambulatory schizophrenics" had a response to drugs which was quite disastrous, in any case.
4. The teenyboppers—we have a tremendous influx of teen-agers to the Haight-Ashbury and the teenybopper segment seems to vary with the season.

It would appear that there is a much greater incidence of acute adverse reactions to LSD in the younger, inexperienced "teenybopper" and in the "prepsychotic" element. As would be expected the prolonged psychotic reactions secondary to LSD occur with greatest frequency in those with previous history of psychiatric problems.

Unfortunately methamphetamine abuse, the major drug problem in Haight-Ashbury, dominates LSD use in the second, third, and fourth categories, heralding a trend from periodic ingestion of LSD to compulsive abuse of methamphetamine.

rate treatment recommendations. Common to both is the supportive care of the "talk down" method.

Supportive care is the recommended approach to the individual who is having panic reaction of the simple-anxiety type. The therapist using the "talk down" method reassures the patient that his distortions will end. Efforts should be made to direct the patient's attention from the environment or the mental aberrations that have precipitated the panic reaction.

Members of the Haight-Ashbury Medical Clinic staff have found that if questions *must* be asked of someone under the influence of LSD, tact is a necessity. Accusations or evidence of fear on the part of a physician or other personnel in attendance will hinder and often negate whatever constructive treatment efforts are made.

Except for a rare subject in a most advanced psychotic state, the LSD user recognizes that his condition results from ingestion of the drug, and he retains some ability to test reality. Consequently most cases can be treated without drugs in a non-threatening setting (in a police sense) and an experienced, sympathetic person must be available to "talk down" the patient. Chlorpromazine can, however, be given orally with good result, but drug therapy alone is inadequate treatment. However, if the patient is in an advanced psychotic state or is extremely agitated, we have found chlorpromazine 50 mg intramuscularly is often required. That drug, in doses of 50 mg intramuscularly or by mouth should be repeated every hour on an as needed schedule, depending on the patient's psychological state.

The "Pink Wedge" Incident, Mass LSD Toxicity and Uncommonly Used Hallucinogens

An instructive example of mass LSD toxicity was observed by the Haight-Ashbury Medical Clinic staff on November 11, 1967, when the "Pink Wedge" was dumped on the market in San Francisco. The pink tablet had sloping edges and was said to contain 1,000 mg of LSD. Chemical analysis proved that the tablet contained 270 mg of LSD and 900 mg of dimethoxymethyl amphetamine. This latter compound is called "STP" on the street (for Serenity, Tranquility and Peace) and is a long-acting hallucinogen producing a much higher incidence of adverse drug reactions.[1,2]

We treated 18 patients with acute toxic psychosis generated by the "Pink Wedge" in a five-hour period. Most of them were having severe panic reactions due to the strength of the preparation, which was more than most of the young persons had been used to.

The patients felt anxious and were unable to think clearly. Some thought that the visual distortions they were experiencing were the way everyone perceived his environment. One girl felt that her hand was purple and that it would remain purple even after she "came down." Reassurances by the clinic staff that this was simply a drug effect alleviated her anxiety. Some of the patients indicated that they felt physically depressed, even though they were not tired, and indicated they felt quite isolated from other people—even from those present who were also under the influence of the "Pink Wedge"—which was an unusual reaction.

Nearly all had a memory lapse, and after they were treated some of the patients returned to the clinic to ask what had happened to them during their trip.

Chronic Physiological Toxicity

At present there is no documented proof of "organicity" after the use of LSD, although certain investigators have described electroencephalographic changes in isolated cases. Some investigators have suggested that "organic brain damage" accounts for these EEG alterations. However, Silverman[3] reported that EEG changes in some chronic LSD users do in fact appear; however, his work with "sensory-perceptual functioning" and EEG "cortical-evoked responses" are not characteristic of brain damage, but suggest other "brain changes" similar to those seen in schizophrenia.

The major debate at present relative to physiological toxicity, however, began when Cohen[4] reported LSD-induced chromosome deformities in tissue culture and alerted the public to the possible correlation of LSD and birth defects. Following this discovery, chromosome breaks were noted in the peripheral white blood cells of persons who had taken LSD.[5,6]

Of greater significance was that the chromosomal breaks in LSD users seem to persist, in contrast to the transient chromosomal breaks seen in such conditions as acute viral infections. The issue was clouded, however, after Loughman[7] found no significant difference in the number of chromosome breaks between the LSD user and appropriate controls. Other negative studies have been published and at present there is no satisfactory answer to the question, "Does LSD cause permanent chromosome damage?"

To confuse the issue further, Cohen, in one of his lectures, described chromosome breaks in persons who had taken amphetamine and chlorpromazine. As the potential for chromosomal breakage has not been evaluated for many drugs, the scientific community must begin the tedious task of studying many therapeutic agents in common use. While this debate was raging, Alexander[8] reported that LSD given to rats in the first trimester of pregnancy produced birth abnormalities in their offspring. Similar observations were made by Auerbach and Rugowski in mice[9] and by Geber in hamsters.[10]

Recently, Zellweger and coworkers[11] reported a birth abnormality in a woman who had taken LSD in the first trimester of pregnancy. However, such an uncontrolled case does little to answer the second major question, "Does LSD lead to birth abnormalities?" Two percent of women give birth to deformed infants naturally and at the clinic no significant increase in infant deformity has been seen although almost all the mothers treated have taken LSD. Only a controlled, large-scale study will answer the question, and the reporting of a single case seems only to add to the confusion.

At present it is obvious that a pregnant woman should not take LSD—but then she should also be cautioned against taking any medication while pregnant, other than those prescribed for specific medical purposes.

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CASE REPORTS

Diagnostic Problems of Partially Treated Whipple's Disease

Report of a Case with Isolated Deficiency of Immunoglobulin M

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ALTHOUGH WHIPPLE'S disease was first described in 1907,[1] it was not until 1947 that the first antemortem diagnosis was made by laparotomy and biopsy.[2] In spite of excellent clinical descriptions of the disease,[3] the diagnosis is frequently not considered until the complete clinical picture has developed or until the characteristic pathologic changes are noted in a biopsy specimen.

The diagnosis becomes even more difficult if some or all of the clinical manifestations are altered or obscured by the use of corticosteroids or short courses of antibiotics for the treatment of other disorders. While Whipple's disease may respond temporarily to corticosteroids, permanent remissions accompanied by the disappearance of the characteristic bacilliform bodies seem to have occurred only after the prolonged use of antibiotics.[4-6] The following case is presented to illustrate the difficulties in making a diagnosis in partially treated Whipple's disease, and also to report an associated dysgammaglobulinemia.

Report of a Case

A 53-year-old Caucasian man was admitted to the UCLA Medical Center in March 1958 for evaluation of profound weakness, fatigue and progressive debility. Nineteen years previously the patient had had an episode of migratory polyarthritis with stiffness and swelling of the knees, ankles, elbows and wrists, but without erythema or increased heat in the joints. The condition had lasted approximately 18 months and then had remitted spontaneously. It was followed by two or three similar episodes, of brief duration. In 1961 night sweats and fever developed, and several months later massive generalized lymphadenopathy was noted. A lymph node biopsy at another hospital was reported as revealing only "reactive hyperplasia." A clinical diagnosis of "low-grade lymphoma" was made despite this histologic report and the patient was treated with a course of corticosteroids for an unknown period. This resulted in decided symptomatic improvement and a decrease in lymphadenopathy. For the next three years the patient remained well and continued to work. In 1964, malaise, fatigue, weakness, chills and fever and the clinical signs of partial obstruction of the small bowel developed. Retroperitoneal lymphadenopathy was demonstrated by lymphangiography

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Supported in part by the Louis B. Mayer Fund for Medical Education and Research.

Submitted 11 February 1969.

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and was presumed to be responsible for the symptoms. Biopsy of a lymph node specimen from the inguinal region again was reported as revealing "reactive hyperplasia." The patient was treated with cobalt-60 irradiation to the abdomen and another course of steroid therapy. He again had a remission of symptoms. In March of 1965 he received a five-day course of erythromycin and in January of 1966 he was treated with 1.2 million units of penicillin G parenterally for upper respiratory tract infections. At the same time, because of gastrointestinal complaints, an upper gastrointestinal series was performed. It revealed a pyloric channel ulcer, for which the patient was treated conservatively with antacids and improved.

In September of 1967, easy fatigability, weakness and fever developed again. A low blood pressure (90/50 mm of mercury) and some bronzing of the skin in areas exposed to the sun were noted. The patient was thought to have Addison's disease and corticosteroids were given again, along with penicillin both orally and parenterally because of low-grade fever. In addition, frequent injections of vitamin B_{12} were given. In October of 1967, he was given a seven-day course of tetracycline by mouth because of symptoms of pleuritis and a respiratory tract infection. His condition did not improve and he began to lose weight. At the same time his hematocrit decreased progressively and in January of 1968 he received two units of whole blood.

The patient denied any history whatsoever of diarrhea or changes in the color and odor of his stools. Several months before admission he had noted palmar erythema for the first time.

Physical Examination: The patient was cachectic but appeared in no acute distress. The temperature was 37.5°C, pulse rate 92 and respirations 24 per minute, and blood pressure 112/60 mm of mercury. The skin was dry with a macular, brownish pigmentation over the upper extremities, especially the forearms. There was no increased pigmentation in the skin folds or areas of trauma, and no spider telangiectasis was seen. A few small, non-tender lymph nodes in the axillary, inguinal and supraclavicular regions were noted. There was also a patchy brown pigmentation on the oral mucous membranes. The tongue was of normal color and well papillated. Examination of the chest revealed generally decreased breath sounds, a prolonged expiratory phase of respiration and basilar rales bilaterally. The heart was slightly enlarged with a grade II/VI high-pitched, blowing, pansystolic murmur, best heard at the apex and radiating to the left axilla. The abdomen was flat, with tympany above and dullness below the umbilicus on percussion. A smooth, firm liver edge was palpable three fingerbreadths below the right costal margin. The spleen tip was palpable at the left costal margin. The right testicle was atrophic. The prostate was symmetrically enlarged without nodules. The joints and extremities were unremarkable except for palmar and periungual erythema. There was no cyanosis, clubbing, edema or neurological abnormality.

TABLE 1.—*Quantitative Immunoglobulins (mg per 100 ml) in Patient With Whipple's Disease*

	First Determination	*Second Determination*	*Normal*
IgG	1.475	2,100	1,200 ±320
IgA	340	288	288 ±121
IgM	<15	21	80 ± 27

Laboratory Data: The hematocrit was 41 percent, the hemoglobin 13.4 grams per 100 ml and the leukocyte count 10,090 per cu mm with 74 percent segmented neutrophils, 4 percent bands, 5 percent eosinophils, 16 percent lymphocytes, 1 percent monocytes and 225,000 platelets. A reticulocyte count was 2.1 percent, the sedimentation rate 37 mm in one hour, the 24-hour urine protein 440 mg, and a creatinine clearance 56 ml per minute. The total serum protein was 7.5 grams per 100 ml with an albumin:globulin ratio of 2.6:4.9. Protein electrophoresis revealed albumin of 37.4 per 100 ml, alpha-1 globulin of 4.7 percent, alpha-2 globulin of 11.2 percent, beta globulin of 12.2 percent and gamma globulin of 34.5 percent. The serum carotene was 41.5 mcg per 100 ml and D-xylose excretion 2.19 grams in 5 hours. The fecal fat excretion was 3.3 grams of fat in 24 hours (three-day collection) and the result of a Schilling test was 2.4 percent. Quantitative immunoglobulins by immunodiffusion technique are listed in Table 1. No paraprotein was detected by gel diffusion immunoelectrophoresis. Gastric analysis revealed no hydrochloric acid during the basal hour and 13.6 mEq per hour of HCl after maximal stimulation with Histalog.®

Pulmonary function tests were compatible with mixed ventilatory insufficiency, predominantly obstructive, consistent with moderately severe emphysema. At gastroscopy with an Olympus GTFA gastrocamera, enlarged rugal folds and an irregular cobblestone appearance of the mucosa of the

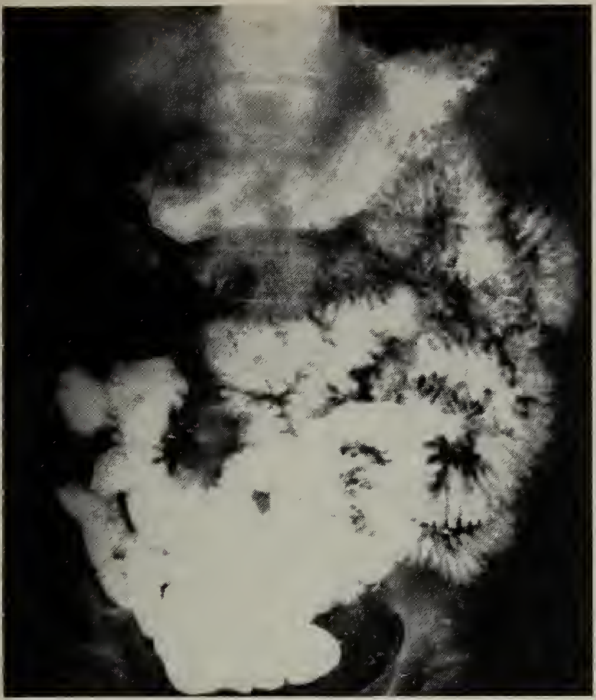

Figure 1.—Roentgenographic demonstration of thickened and widened mucosal folds in small bowel.

greater curvature of the stomach were noted.

Results of the following studies were within normal limits: routine urinalysis, serum sodium, potassium, chloride, bicarbonate, calcium, SGOT, SGPT, LDH, alkaline and acid phosphatases, and bilirubin, prothrombin time, oral glucose tolerance test, urinary sodium and potassium, 24-hour urinary 17-hydroxy and 17-ketosteroids before and after ACTH stimulation, febrile agglutinins, VDRL, partial thromboplastin time, PBI and T-3 uptake, a Sabin-Feldman dye test, bone marrow aspiration, gastric cytology and stool guaiac.

Radiologic Examinations: Radiographs of the chest showed calcifications in the perihilar nodes and mild left ventricular enlargement. Residual contrast medium in the periaortic nodes from the previous lymphangiogram performed in 1964 was seen on abdominal films. There was not enough medium remaining to be diagnostic of lymphadenopathy at this time. Upper gastrointestinal and small bowel series revealed gastric rugal hypertrophy and thickening and widening of the mucosal folds of the small intestine, most pronounced in the jejunum (Figure 1). Liver and spleen scans revealed only mild splenic enlargement.

Pathologic Data: The lymph node biopsy from previous admission to an outside hospital in 1964 was reviewed and stained with PAS. Histiocytes containing PAS-positive granules were scattered throughout the node. A foreign body reaction consisting of giant cells and lipophages around cystic areas was also noted and presumed to be ascribable to the lymphangiogram procedure. A peroral small bowel biopsy revealed short and thickened villi, containing numerous macrophages engorged with eosinophilic, PAS-positive cytoplasmic material. There was acute inflammatory infiltrate throughout the lamina propria (Figure 2). A rectal biopsy revealed scattered histiocytes in the lamina propria containing abundant granular PAS-positive material. Prolonged cultures of a piece of the small bowel biopsy specimen did not grow any anaeorbic organisms.

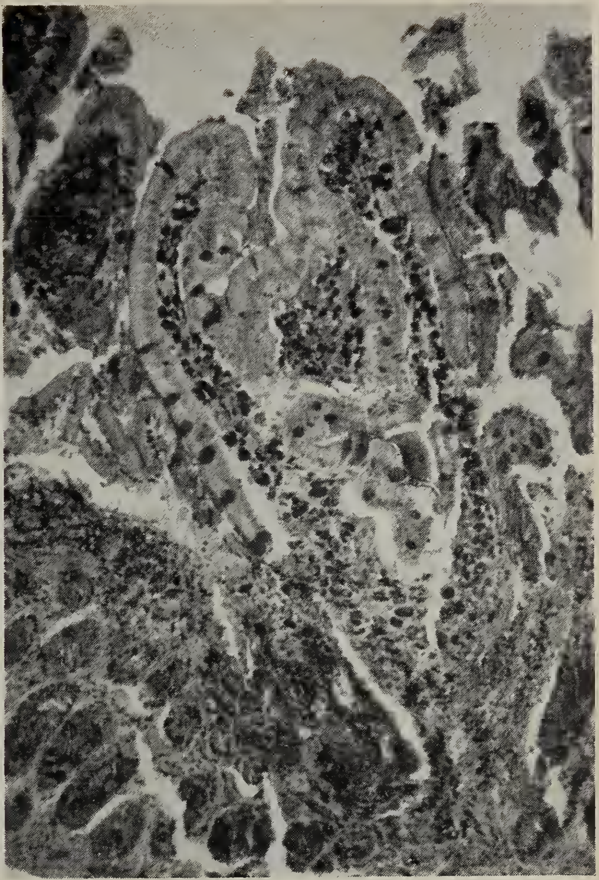

Figure 2.—Photomicrograph of jejunal mucosal biopsy specimen demonstrating PAS-positive macrophages in the lamina propria, X 100 X 4.

Immunofluorescent studies of a rectal biopsy specimen for immunoglobulins A and G as well as secretory IgA showed no definite abnormality. No cells containing IgM could be identified, however.

Discussion

Whipple's disease, originally considered a degenerative or malignant disorder, is now believed to be an infectious disease.[5] The clinical and pathologic manifestations have been reported in great detail by many investigators.[1,2,3,7,8] Laboratory and radiographic abnormalities resemble those commonly seen with malabsorption syndromes. While the characteristic PAS-positive, granule-containing macrophages are present in the lymph nodes and lamina propria of the small bowel, the disease is not confined to only these tissues.[7,9,10] On electron microscopy bacilliform bodies measuring 0.25 x 1.5 microns, which disappear after adequate antibiotic therapy, are seen.[4-6] Therapy with corticosteroids alone may result in remission, but relapse and a progressive downhill course usually follow. A two-week course of procaine penicillin and streptomycin followed by 1 gram of tetracycline per day for one year usually results in permanent remission. That is the current regimen of choice.[11,12]

Nowadays many patients, like the one presented here, are treated with corticosteroids and broad-spectrum antibiotics for a variety of conditions, often with marginal indications. As a result, the manner of onset of Whipple's disease may be changed and the clinical signs and symptoms may be obscured. The first manifestations of Whipple's disease in the present case may have been the migratory polyarthritis which was noted 19 years before admission. Arthralgia or arthritis or both occur in the majority of patients and have been known to precede the gastrointestinal symptoms by many years.[13] In the present case, 12 years after the episode of polyarthritis, fever, lymphadenopathy and a variety of non-specific complaints led to a mistaken diagnosis of lymphoma, which seemed to respond dramatically to a course of steroids. Three years later, in 1964, the patient again had good response to corticosteroids and irradiation. During the subsequent three years he received steroids for a presumptive diagnosis of Addison's disease, as well as multiple courses of a variety of antibiotics for respiratory tract infections and pleuritis. It is noteworthy that he had no history of diarrhea and no laboratory evidence of steatorrhea, although D-xylose and B_{12} absorption were impaired. Three of the 12 patients reported by Chears and coworkers also had no diarrhea and one of eight had no steatorrhea.[3]

The absence of anemia in this patient was probably due to frequent vitamin B_{12} injections and the two blood transfusions.

There are many features of the history in the present case that in restrospect are quite typical of Whipple's disease: the patient is a middle-aged Caucasian man with a history of arthritis and arthralgias, lympadenopathy, mild splenomegaly, hypotension and pigmentation, as well as chills, fevers and loss of weight. The cardiac murmur may be related to Whipple's disease, since vegetations have been noted on cardiac valves at autopsy.[7,14] The x-ray examinations of the gastrointestinal tract were certainly consistent with diffuse small bowel disease. The abnormal gastric mucosa may be attributed to infiltration with either PAS-positive histiocytes or inflammatory cells.

Pronounced reduction in IgM level was noted on two separate determinations. A host abnormality was previously suggested by the slight reduction of IgM globulin noted by Maxwell and coworkers, although the actual IgM level was not mentioned.[15] This isolated IgM deficiency also has been recently reported in some cases of non-tropical sprue.[16] The absence of IgM-containing cells on rectal biopsy may support this serum abnormality. However, the significance of the lack of IgM staining is not known at this time.

The use of broad-spectrum antibiotics and corticosteroids for many non-specific illnesses may change the clinical manifestations and natural history of Whipple's disease. Before dismissing the diagnosis of this disorder for lack of clinical evidence, the effects of such previous therapy must be taken into account in patients with obscure signs and symptoms.

Summary

A case of Whipple's disease is presented in which the previous use of corticosteroids and broad-spectrum antibiotics masked the classical clinical manifestations, illustrating the diagnostic difficulties of this disease in the modern era. An associated IgM deficiency was also detected in this case.

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PREDNISONE IN GLOMERULONEPHRITIS

"For patients with diagnosed glomerulonephritis, I would choose first a trial on prednisone. One thing I want to call attention to is the use of intermittent dosage — the so-called 48-hour schedule where a single dose of prednisone is given every 48 hours — [versus the use of daily dosage].

"In the beginning, one is better off giving a *daily* dose, preferably with the patient in the hospital where his condition can be followed closely. . . . One can learn the type of lesion or the resiliency of the lesion much better by starting off with a low daily dosage and pushing it up. When the lesion is under control is the time to see if one can shift to an *intermittent* dosage. The reason I mention the intermittent dosage is that the side-effects are so much fewer; and you can often push the dose up to 200 mg of prednisone every 48 hours. . . . One word of caution about intermittent dosage: you can't always get away with it in systemic lupus [erythematosus]. I've seen patients, and I'm sure everyone has, in whom . . . you have to use a daily dosage. They start getting symptoms when they're on the intermittent dosage. But if you can get away with it, it is well worth using."

—JAMES HOPPER, JR., M.D., San Francisco
Extracted from *Audio-Digest Internal Medicine,* Vol. 15, No. 24, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

Carcinomatous Neuromyopathy

The Non-Metastatic Effects of Cancer on the Nervous System

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■ *Cancer can produce a variety of effects on the nervous system either by direct compression or invasion, or remotely by some as yet unknown metabolic, toxic, viral or immunologic effect on the nervous system. The neurologic effects associated with cancer that does not directly involve neural tissue have distinctive features that can give the first clue to a previously undiagnosed neoplasm. Physicians who see patients with neurologic illness should be aware that there may be an underlying malignant lesion giving rise to the neurologic syndrome; and conversely they should be on the alert for neurologic complications in patients with known cancer even though the lesion does not directly press upon or invade nerve tissue.*

It is not unusual for diseases primarily affecting one organ to have secondary effects on others. For example, heart disease may have secondary effects on lungs, liver, kidney. Secondary effects are perhaps even more striking in cancer. Many syndromes have been described associating malignant lesions with organ derangement outside their primary site of growth. Hematologic, dermatologic, endocrine, gastrointestinal, skeletal and metabolic abnormalities may be seen in association with tumors. It is the nervous system, however, which seems particularly vulnerable to the ill effects of a distant malignant lesion. Syndromes affecting various levels of the central nervous system, peripheral nervous system and myoneural junction, as well as muscle itself, have been reported. We will deal here with some of the effects that a distant malignant tumor may have on the nervous system. In the following discussion, it is assumed that direct metastasis to neural tissue is not present.

History

In 1888 Oppenheim[1] first reported an association between a neurologic syndrome and a distant malignant lesion. It is of interest that he suggested that the neurologic manifestations were the result of some unknown toxic process—an explanation that is still "modern" but is no more illuminating today, more than three-quarters of a century later, than it was then. Several reports in the European literature followed Oppenheim's study, but none added very much to the clinical description or to the understanding of either etiologic or pathologic factors in this association.

New interest was generated in these syndromes in 1948 when Denny-Brown[2] reported two patients with bronchogenic carcinoma and primary degeneration of the dorsal root ganglion cells. Both patients presented with numbness and sensory loss in the extremities. In addition there was primary degeneration of the muscles, that is, "polymyositis." Denny-Brown proposed that the neurologic and muscular manifestations were probably on a metabolic basis and suggested a similarity to exper-

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imental pantothenic acid and vitamin E deficiency in animals.

Since that report, a great number of papers have appeared testifying to the more than casual relationship between neurologic syndromes and a distant malignant lesion. Lennox and Prichard[3] pointed out the frequent association between peripheral neuropathy and cancer of the lung. Brain and coworkers[4] described the syndrome of cerebellar degeneration in association with carcinoma. In 1958 Åström and coworkers[5] brought attention to the syndrome of progressive multifocal leukoencephalopathy and indicated its close relationship to chronic lymphatic leukemia and Hodgkin's disease.

With these milestones behind, there has been an increasing number of reports further elucidating clinical syndromes, but even so very little has been brought out to explain the basic mechanisms.

Incidence

The incidence of only certain forms of carcinomatous neuromyopathy is known. For most of our information on this subject we are indebted to Croft and Wilkinson.[6,7] These British investigators studied 1,476 patients with cancer. The incidence of all forms of carcinomatous neuromyopathy is indicated in Table 1. About 7 percent of all patients with cancer have been found to have neurologic findings in association with a distant malignant lesion. The highest incidence occurs in cancer of the lung, ovary and stomach. It is to be noted that only solid tumors were studied. The frequency of neurologic manifestations in patients with blood dyscrasias, leukemia, lymphosarcoma and others was not included. Although precise statistics on the frequency of neurologic manifestations in such patients are not available, experience in a large cancer hospital suggests that the incidence of neurologic manifestations in these diseases is extremely high and may be in the order of magnitude of 15 to 20 percent.

TABLE. 1.—*Types of Neuromyopathy in Survey of 1,476 Patients with Cancer (After Croft and Wilkinson,[7] 1965)*

Site of Cancer	*Sex*	*No. of Patients*	*With Neuropathy No.*	*Percent*
Lung	M	250	40	16.0%
	F	69	9	13.0
Breast	F	250	11	4.4
Prostate	M	31	2	6.4
Ovary	F	55	9	16.4
Uterus	F	76	1	1.3
Cervix	F	149	3	2.0
Stomach	M	123	10	8.1
	F	58	8	14.0
Colon	M	61	3	5.0
	F	99	4	4.0
Rectum	M	114	1	0.8
	F	93	0	0.0
Double Primaries	M&F	48	2	4.2
		1,476	103	7.0%

If we apply the British statistics to the United States population, we come up with some rather surprising statistics. It is estimated that 315,000 persons died of cancer in the United States in 1968.[8] If 7 percent of that number have neurologic manifestations of a distant malignant lesion and if they each live for only one year, then approximately 22,000 Americans will be found to have an associated neurologic syndrome at all times.

Table 2 groups the various forms of carcinomatous neuromyopathy into rather broad categories and indicates the relative frequency of the different varieties found in the study of 1,476 patients. Two hundred hospital control patients

TABLE 2.—*The Incidence of the Different Types of Neuromyopathy in the Series of 1,476 Patients with Proved Cancer (After Croft and Wilkinson,[7] 1965)*

Site of Cancer	*Sex*	*Total*	*Neuro-muscular*	*Poly-neuritic*	*Sensory Neuropathy*	*Cerebellar*	*Motor Neuron*	*Myas-thenic*	*Mixed*	*Other*
Lung	M	40	33	4	0	2	0	0	1	0
	F	9	5	1	0	0	2	0	1	0
Breast	F	11	6	2	0	0	0	1	1	1
Prostate	M	2	2	0	0	0	0	0	0	0
Ovary	F	9	7	0	0	1	0	1	0	0
Uterus	F	1	1	0	0	0	0	0	0	0
Cervix	F	3	3	0	0	0	0	0	0	0
Stomach	M	10	4	3	0	0	1	0	2	0
	F	8	5	1	0	0	0	0	1	1
Colon	M	3	1	2	0	0	0	0	0	0
	F	4	3	1	0	0	0	0	0	0
Rectum	M	1	1	0	0	0	0	0	0	0
	F	0	0	0	0	0	0	0	0	0
Double Primary	M&F	2	1	1	0	0	0	0	0	0
Total		103	72	15	0	3	3	2	6	2

without cancer were examined. Two percent of the 200 patients were found to have reflex abnormalities which in a patient with carcinoma might suggest a minor degree of neuromyopathy. It was further found in this study that "the incidence of neuromyopathy in carcinoma of the lung and breast was not related to the age of the patient, the duration of the symptoms of cancer, the amount of weight loss or to the patient's blood group."

Etiology

As previously indicated, Oppenheim[1] in 1888 believed that the neurologic manifestations of a distant malignant lesion were due to some metabolic or toxic effect originating from the primary tumor. We have not come very far in our understanding of the basic mechanism since that time. Denny-Brown[2] suggested that it may be caused by a vitamin deficiency. Hart[9] reported two cases of cancer and proximal motor neuropathy which he felt were owing to vitamin B deficiency, particularly pyridoxine. Although the carcinoma was untreated, both patients had amelioration of their neurologic syndromes following administration of vitamin B complex. Although it is possible that avitaminosis may accompany malignant states, thereby producing neurologic syndromes, the usual form of carcinomatous neuromyopathy is not likely to be caused by a vitamin deficiency. We have had ample opportunity to realize that the mere administration of vitamin B and other vitamins does not usually produce any beneficial effect in these patients. More recent chemical studies have also failed to demonstrate such an association.[10]

The possibility of viral infection cannot be excluded. The rather high incidence of non-metastatic neurologic complications associated with lymphomas brings to mind the suggestion that in some of these tumors there may be a viral etiologic factor. Henson, et al,[11] suggested viral infection as a possible cause of cerebellar degeneration and sensory neuropathy. Their hypothesis was based on the similarity of the neuronal changes seen on postmortem examination in these patients to the changes in the nervous system induced by experimental viral infections.

The neurologic syndrome in this group of diseases with the strongest evidence for a viral infection is progressive multifocal leukoencephalopathy. This is based primarily on the neuropathological appearance of the lesion.[12,13] However, up to this time no virus has been grown either from spinal fluid or fresh frozen brain tissue obtained at autopsy.

As to a metabolic or toxic effect on the nervous system, there have been no firm biochemical findings to substantiate this hypothesis, although it is a reasonable explanation and perhaps the one that best fits with the known facts concerning these syndromes.

The final consideration is that of hypersensitivity or immunologic reaction. There is some tentative evidence in the literature for an abnormal immune mechanism in dermatomyositis.[14,15] There is also evidence to suggest that an immunologic response may be an etiologic factor in myasthenia gravis.[16] Perhaps more to the point is the finding by Wilkinson[17] of antibrain antibodies in patients with carcinomatous sensory neuropathy. (See below).

Importance of the Problem

It has been pointed out that approximately 7 percent of patients with malignant disease will have neurologic manifestations without tumor being in direct contiguity with the nervous system. However, experience indicates that the diagnosis rate in this country is considerably less than the frequency with which it occurs. This may be because some of these syndromes are quite subtle and require a certain degree of neurologic sophistication for diagnosis. It is more probable, however, that the medical community has not been sufficiently alerted to watch for these syndromes.

The importance of recognizing these syndromes lies first of all in the fact that they may be the earliest sign of an underlying malignant disease. The neurologic manifestations may occur many months and sometimes even years before the neoplasm is discovered.

Second, these neurological manifestations must be differentiated from metastatic disease to the nervous system. Familiarity with their recognition may be very important in deciding the course of a patient's treatment and may also be a valuable prognostic indicator. Certain syndromes characteristically are associated with a remote malignant lesion, but of course not all neurologic disabilities in association with cancer are the result of a non-metastatic effect of the tumor. In fact such cases represent a relatively small proportion of all the neurologic effects which may occur in patients with an underlying malignant disease. A careful evaluation is often necessary to decide whether the neurologic findings represent one of the remote effects or are ascribable to direct invasion or compression of the nervous system by tumor tissue.[18]

The third important consideration is the effect of treatment of the underlying malignant disease on the course of the neuromuscular disorder. Although no statistics are available, experience has shown that occasionally striking remissions of the neurologic symptoms occur when the underlying lesion is treated. Unfortunately, this is not uniformly the case. However, the effect of treatment is unpredictable and we, as well as others,[19] have seen many instances in which dramatic improvement in the neurologic status occurred when the underlying tumor was treated by x-rays, surgical operation or chemotherapy.

Illustrative Case History

A 53-year-old right-handed tile setter was first seen in July 1966 with chief complaint of difficulty in walking of about six months' duration.

He had apparently been in good health until December 1965, when he began to notice numbness and tingling in his left leg. Shortly thereafter weakness developed in that leg, making walking difficult. Similar symptoms began on the right three months later. There were no symptoms referable to the upper extremities. The patient had had no coordination difficulties and no complaints referable to the urinary tract. He had lost 35 pounds in the previous year.

Past medical history indicated that he was a fairly heavy drinker most of his life but had not taken alcohol since he had been found to have diabetes mellitus, in December 1965. The diabetes was relatively mild and was treated with diet and tolbutamide (Orinase®). Family history was not contributory.

General medical examination showed evidence of recent weight loss. The edge of the liver was palpable 3 cm below the right costal margin. The liver was firm and not tender, and no nodules were felt. The spleen was not palpable.

On neurologic examination the head and neck were normal and mental status was within normal limits. The sense of smell was intact. Examination of the fundi showed evidence of old exudates bilaterally. Discs were unremarkable. The pupils reacted poorly to light and better to accommodation. Both pupils were slightly irregular. Extraocular movements were normal. Facial sensation and corneal reflexes were intact. No facial weakness was present. There was a mild decrease in conductive hearing bilaterally. The ninth, tenth and eleventh cranial nerves were normal. There was a slight degree of atrophy over the left side of the tongue, and the tongue deviated to the left on protrusion. The left genioglossus muscle was also weakened. No fasciculations or fibrillations of the tongue were seen.

Motor System: The upper extremities showed only the generalized wasting of recent weight loss. In the lower extremities there was diffuse atrophy of both legs, of the left more than the right. Generalized weakness was noted. It was more or less symmetrical and was about equal distally and proximally. There was a slight suggestion of spasticity in the lower extremities but this was not definite. Deep tendon reflexes were normal in the upper extremities and absent in the lower extremities. The Babinski sign was positive on the left, equivocally present on the right. No abnormality of coordination was noted. On sensory examination there was decreased perception of pin and touch in a stocking distribution in both lower extremities. Sensation of position and vibration was depressed below the hips. The saddle area was not involved. In the upper extremities, all sensory responses were normal.

Stance and Gait: The patient walked with a broad-based somewhat slapping gait with the aid of a crutch and a cane. Romberg's sign was present.

Laboratory Studies: Results of routine blood and urine analysis were within normal limits, as was the sedimentation rate. Blood VDRL was nonreactive. The response to a glucose tolerance test was mildly abnormal. Spinal fluid examination showed an opening pressure of 160 mm of water and no cellular response. Protein content was 147 mg and sugar 61 mg per 100 ml of fluid. Colloidal gold revealed a mid-zone curve and the spinal fluid VDRL report was negative. T3 and T4 tests for thyroid status were normal. Gastric acid analysis following histolog stimulation was normal. No abnormalities were seen on x-ray studies of the chest and skull. Barium enema and upper gastrointestinal studies were normal except for the demonstration of pronounced gastric dilatation which was thought to be compatable with visceral neuritis. An electroencephalogram was within normal limits, as was an electrocardiogram.

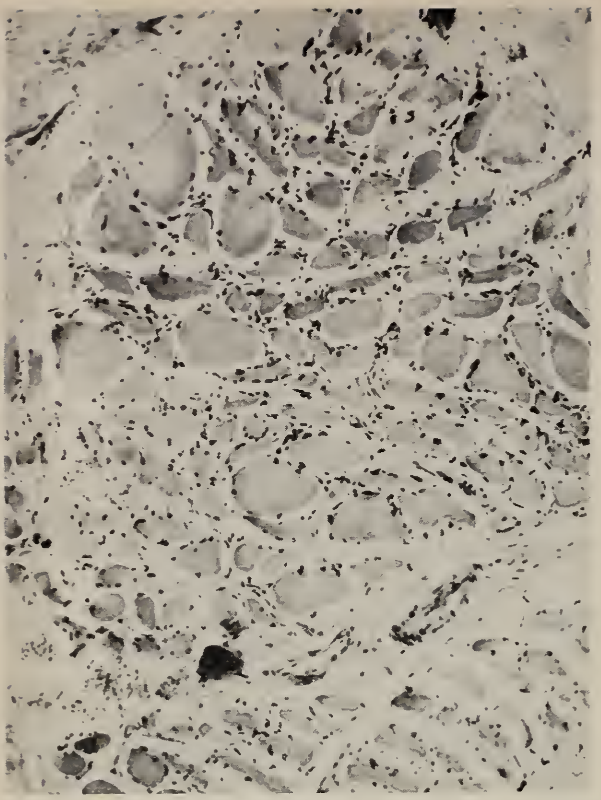

Figure 1.—Muscle biopsy illustrating mixed neuropathic and myopathic features (× 90).

An electromyogram showed evidence of both a neuropathic and a myopathic process as revealed by diffuse fibrillations in both lower extremities as well as polyphasic, bizarre motor units in all muscles of the legs. The upper extremities were unremarkable. Nerve conduction times of the peroneal nerves were decidedly depressed. An oil myelogram showed mild cervical spondylosis. Muscle biopsy of the left quadraceps showed atrophic fascicles, clumping of sarcolemmal nuclei, enlarged and ballooned muscle fibers. There was no evidence of angiopathy or fibrosis. The skin was unremarkable. The findings were interpreted as those of mixed neurogenic and myopathic atrophy (Figure 1).

Because of the mixed findings of peripheral neuritis and myopathy, an occult neoplasm was strongly suspected but could not be confirmed at that time. Other possibilities included diabetic neuritis and amyotrophy, and alcoholic neuritis, but these seemed much less likely than occult neoplasm.

When the patient was seen again three months later, the neurologic findings had progressed. There was beginning involvement in the upper extremities. On general examination a tumor was noted on the left side of the tongue. Biopsy showed it to be anaplastic carcinoma. Cobalt teletherapy was applied to the tongue and to cervical nodes.

The patient died of widely disseminated metastatic disease four months following the diagnosis of carcinoma of the tongue. However no invasion or compression by tumor in either the central or the peripheral nervous system was found. Peripheral nerves showed Wallerian degeneration and segmental demyelination.

Comment: This patient had neurologic symptoms nine months before the diagnosis of an anaplastic carcinoma of the tongue. The neurologic manifestations were highly suggestive of an occult neoplasm but none could be found until four months before death. In retrospect the deviation of the tongue on the initial examination probably was a result of a deep and slowly growing tumor within the tongue, but it was not recognized as such at that time. When the neoplasm became obvious and treatment was begun, the tumor was well advanced and the patient eventually died of widespread metastasis to all major organs except the nervous system. The neurologic symptoms progressed during the period of treatment.

TABLE 3.—*Classification of Neurologic Manifestaion of Distant Malignant Lesions*

I. Supra-tentorial
  a. Dementia
  b. Progresive Multifocal Leukoencephalopathy
II. Infra-tentorial
  a. Subacute Cerebellar Degeneration
  b. Brain Stem Syndromes
III. Myelopathy
  a. System Disease
  b. Transverse Myelopathy
  c. A.L.S.
IV. Neuropathy
  a. Sensory
  b. Mixed
  c. Mononeuritis
V. Muscle
  a. Neuromyopathy
  b. Myasthenic Syndromes
  c. Polymyositis
VI. Mixed

Classification

A simplified classification is offered in Table 3. This relates the neurologic manifestations to anatomic levels. Pure and complete forms of the neurologic manifestations of distant lesions are not uniformly seen. Incomplete manifestations and mixtures of several types are perhaps more common than isolated syndromes. Although the association between an occult malignant tumor and neurologic disorder has been known for three-quarters of a century, this relationship has not been well known to the medical community. The challenge of discovering new syndromes and new variants on previously described themes is very real. Included in the evaluation of a patient with perplexing neurologic disease of unknown cause should always be a consideration of occult malignant disease even if the specific neurologic findings do not coincide with previously reported syndromes. The field is still relatively new and the opportunity for fresh observations is still at hand.

Specific Types

Specific types of neurological changes associated with distant malignant lesions are of five general orders:

I. Supra-tentorial

Dementia

Dementia, as well as changes in personality, is fairly common in association with malignant disease, particularly when the disease is far advanced. It may be seen in association with other neuromyopathic states, or it may occur independently.[20,21] Charatan and Brierley[22] reported three patients with carcinoma of the lung who had confusional psychosis of a fluctuating nature. No significant neuropathological findings were seen on postmortem examination in these patients.

Brain and Henson[23] found dementia or an organic psychosis in 17 of 42 patients with neurologic complications of carcinoma. Again, no neuropathologic basis was found. Most of the patients had simple dementia of varying severity.

Dementia occurring in severe systemic disease is a rather non-specific effect and is seen not only with neoplasms but in other metabolic disorders, such as renal failure, as well.[24] It is also common in clinical experience to see varying degrees of dementia and psychological abnormalities in advanced heart failure, pulmonary disease and a variety of other systemic illnesses. However, in association with a malignant disease it may occur early in the course when the patient is still in good clinical condition. There is nothing unique about the dementia occurring with a remote malignant lesion to distinguish it from the dementia that occurs in association with other systemic disorders. Furthermore no specific pathologic abnormalities have been observed in patients with this problem. Clinical experience has indicated that the dementia or toxic psychosis can sometimes be ameliorated by treatment of the underlying malignant disease.

Progressive Multifocal Leukoencephalopathy

This condition, first described in 1958 by Åström, Mancall and Richardson,[5] is a disorder of cerebral white matter. It is a well studied neuropathologic entity. The basic pathologic feature is a demyelinating process which occurs in widely separated areas of the central nervous system. There is destruction of myelin sheaths with relative preservation of central axis cylinders. The lesions vary in size from microscopic to large areas of myelin destruction. They vary in location from case to case and the clinical manifestations are a reflection of the geography of these lesions. As the name implies it is a progressive disease leading to death in a few weeks to a few months. It is seen only in adults, no proved case having been reported in a child. The incidence is about twice as high in men as in women. Paralysis, visual field defects or blindness, aphasia, ataxia, dysarthria, dementia and finally coma is the usual neurologic sequence of events. As would be expected in a primarily white matter disease, convulsions are rare, although they have been reported.[25]

When first reported, the syndrome seemed to be associated primarily with chronic lymphatic leukemia and Hodgkin's disease. Since then, however, it has been seen in a variety of other conditions including other lymphosarcomas, myeloproliferative disorders and non-neoplastic disorders such as sarcoidosis and tuberculosis. It has also been reported in Whipple's disease, primary hypersplenism and a variety of other miscellaneous conditions.

As was previously noted, there are some suggestions, primarily on pathologic grounds, that progressive multifocal leukoencephalopathy may have a viral cause, although a specific virus has never been isolated. The cerebrospinal fluid is usually normal and other laboratory investigations are not very rewarding. It is a difficult diagnosis to make during life, but it should be considered in a patient who has reticulosis or other chronic disease and begins to have neurologic symptoms suggesting white matter dysfunction. The symptoms may at first mimic those of a brain tumor, but laboratory investigations will show no mass present. Corticosteroids have not been shown to be useful in the treatment of this condition.

II. Infra-tentorial

Subacute Cerebellar Degeneration

In 1919 Brouwer[26] described a patient with cerebellar ataxia and a "polymorphic sarcoma of the pelvis." However, it was not until 1938 that a causal relationship between the tumor and the neurologic impairment was first suggested, by Brouwer and Bymand.[27] Most of the more recent information concerning this syndrome comes from Brain and his coworkers.[28,29]

The condition is not common and up to 1965 only about 30 pathologically verified cases had been reported in the literature. However, the clinical symptoms are rather striking and it seems clear that there are many more cases occurring than the rather sparse literature on the subject would lead one to believe.

All patients show ataxia of pronounced degree—usually of all four extremities, but occasionally confined to either the upper or lower limbs. Almost all patients have severe dysarthria, making their speech difficult to understand or unintelligible. Nystagmus is not a prominent feature, but may be seen occasionally. Other neurologic symptoms occur to a lesser degree. There is occasionally difficulty in swallowing, ptosis, generalized weakness, paresthesia, deafness, diminution or absence of deep tendon reflexes, extensor plantar responses, and occasionally dementia.

The cerebrospinal fluid is usually unremarkable although mild pleocytosis sometimes occurs. The spinal fluid protein may also be slightly elevated. Paretic colloidal gold curves have been reported in several cases.

The highest occurrence rate is in the sixth decade of life and the division between sexes is about equal. There have been no reported cases in children. The neoplasm is most likely to be in the lung and next most frequently in the ovary and breast. Brain[30] reported 17 cases, in seven of which the patients were known to have a preexisting neoplasm. The interval between symptoms of the neoplasm and those of the neurologic disease ranged from three to twenty-four months. In ten cases the central nervous system disorder preceded the discovery of the neoplasm by from two to thirty-six months.

The pathologic changes are characterized by a severe loss of Purkinje cells, as well as some degeneration of the molecular and granular layers of the cerebellum. Degeneration of the long tracts of the spinal cord have been reported in several cases, particularly the spino-cerebellar tracts and dorsal columns. Degeneration of other areas of the brain stem may also be seen and it accounts for the ptosis, ophthalmoplegia, muscle weakness, change in reflexes and the other neurologic findings. Remissions in the neurologic syndrome in some cases have been reported with treatment of the underlying malignant lesion.

Brain Stem Syndromes

Brain stem symptoms may occur in connection with any of the previously described syndromes (dementia, progressive multifocal leukoencephalopathy or subacute cerebellar degeneration). Ophthalmoplegia, nystagmus, dysarthria, bulbar palsy and sensory abnormalities may all occur as a result of lesions of the brain stem.

A somewhat more specific brain stem abnormality has been reported in association with carcinoma. It was first described by Henson, Russell and Wilkinson,[31] who reported two patients with carcinoma and neurologic signs referable to the brain stem and spinal cord. On postmortem examination evidence of chronic progressive poliomyelitis was noted. An inflammatory reaction was seen about the brain stem and portions of the spinal cord. The investigators thought that perhaps a virus was responsible and they called the condition "encephalomyelitis." The condition is rare. The clinical symptoms correlate with the site of the pathologic process. A sensory neuropathy may be present because of involvement of the dorsal root ganglia. The duration of the neurologic illness is usually from six to twenty-four months. The active phase of encephalomyelitis may burn out after several months, although in some cases it may continue until death. There are only about a dozen such cases reported in the literature and in most of them the associated malignant lesion was cancer of the lung.

III. Myelopathy

System Disease

Spino-cerebellar or posterior column degeneration may be seen in association with subacute cerebellar degeneration but may also present as the dominant neurologic feature in patients with an occult neoplasm. We have seen several patients with neurologic abnormalities resembling "combined system disease" of pernicious anemia with posterior and lateral column involvement but without other clinical manifestations or laboratory evidence of pernicious anemia, either hematologic or neurologic. The neurologic abnormalities did not respond to B^{12} therapy.

Transverse Myelopathy

This is a rapidly progressive necrotizing process of the spinal cord and is unlike either the secondary changes in the cord seen with neuropathy or the systemized tract degenerations associated with cerebellar degeneration.

The patients usually have a rapidly progressive ascending sensory and motor deficit which terminates in death in a matter of a few days or weeks. In most reported cases the thoracic cord has been the most severely affected. Both the grey and the white matter are destroyed by a necrotic process without evidence of metastasis within the substance of the central nervous system.[32]

Amyotrophic Lateral Sclerosis

In 1965 reports of two series were published in which an association was noted between amyotrophic lateral sclerosis (ALS) and an underlying neoplasm. Norris and Engle[33] found 10 percent of 130 consecutive patients with ALS had an associated neoplasm. Brain and coworkers[34] reported on 11 similar patients. Clinical examination of these patients revealed fairly typical amyotrophic lateral sclerosis with widespread lower motor neuron disease, weakness and fasciculations, as well as evidence of pyramidal tract disease. In the patients with carcinoma several departures from the classical characteristics of ALS were noted. The male to female sex ratio was higher among them and ALS developed at an older age than does classical ALS. Moreover the course of the neurologic illness seemed to be more benign than in the usual form of ALS. Perhaps most importantly, many of the patients with an underlying neoplasm had mild degrees of sensory loss, particularly of vibratory and position sense. Classical ALS is thought not to have any significant impairment in sensation.

Two patients in the Brain[34] series were observed at autopsy to have extensive degeneration of the anterior horn cells and lateral columns, which mimicked very closely the pathologic changes of classic ALS. In addition, however, there was a mild degree of degeneration of the posterior columns and this correlated well with the sensory findings during life.

Dyck[35] could not confirm the high incidence of cancer in association with amyotrophic lateral sclerosis. Our own experience indicated a higher association between ALS and cancer than had previously been recognized, but it did not approach the 10 percent of all ALS patients reported by Norris and Engle.[33] We observed one patient with cancer of the ovary and associated ALS who had moderate improvement in neurologic findings after surgical and cobalt treatment of the underlying tumor.

IV. Neuropathy

Sensory Neuropathy

As was previously indicated, Denny-Brown's[2] report in 1948 of two patients with sensory neuropathy stimulated renewed interest in the entire field of carcinomatous neuromyopathy. Pure sensory neuropathy is quite rare. However, the clinical manifestations in these patients are striking, with rapidly progressive and severe sensory deficit in all extremities producing decided sensory loss and sensory ataxia. Pathologic changes noted in such cases are pronounced destruction of the posterior root ganglia and associated posterior column degeneration. Wilkinson and Zeromski[36] also noted inflammatory lesions in the brain stem and limbic cortex in some cases. The peripheral nerves also show considerable demyelination.

This group of patients is of particular interest because immunofluorescent detection of antibodies against neurons has been demonstrated in several patients with sensory carcinomatous neuropathy.[17,36] Croft and coworkers[37] demonstrated the presence of circulating organ-specific antibrain antibodies in serum specimens from four patients with sensory neuropathy associated with bronchial carcinoma, and in cerebral spinal fluid of two of these patients. It is only in association with sensory neuropathy that evidence highly suggestive of an immunologic type-specific reaction has been demonstrated. Although similar serum investigations have been done in other forms of carcinomatous neuropathy, they have failed to demonstrate clear-cut evidence of immunologic response. This raises several interesting possibilities, among which is whether the different varieties of carcinomatous neuropathy may not have different etiologic factors. It also suggests the possibility of utilizing immunosuppressant agents in the treatment of carcinomatous sensory neuropathy.

Mixed Sensorimotor Neuropathy

This is the most frequent kind of carcinomatous neuropathy, making up 15 to 30 percent of the total.[38] Croft and coworkers[39] found that cases of this kind could be divided into three clinical types. In the first group were patients with known malignant disease in whom a mild peripheral neuropathy developed as a terminal manifestation of the underlying malignant disease. The second group consisted of patients with severe peripheral neuropathy of either subacute or acute onset who often were first seen because of neurologic symptoms, the tumor being found during investigation for the neurologic condition. The third group were similar to the second but the neuropathy followed a remitting and sometimes relapsing course, not necessarily associated with the course of the underlying malignant disease.

Pure sensory neuropathy occurs almost exclusively with carcinoma of the lung; and the sensorimotor form is associated with lung cancer in about 50 percent of the cases in which this form is found, but it may also occur with a wide variety of neoplasms elsewhere in the body. The oat cell variety is most frequent. In group two, the longest interval between the development of neurologic symptoms and the discovery of the underlying tumor was three years and ten months.

The clinical features cannot be distinguished from those of other kinds of sensorimotor peripheral neuropathy. The syndrome frequently begins with parethesias in the distal portions of the extremities. Muscle weakness, atrophy, fasciculations and decreased reflexes are noted on examination.

About two-thirds of the patients have elevations of spinal fluid protein and about one-third have abnormalities in the colloidal gold curve. There is no significant cellular response in the spinal fluid. Pathologically the change observed in peripheral neuritis is most likely to be segmental demyelination with relative preservation of the axis cylinder. This suggests a better prognosis than if the reverse were true. Nerve conduction studies are usually abnormal and, according to Moody,[40] in some patients electrophysiological tests showed abnormalities before the neurologic syndromes became clinically apparent.

The syndrome of mixed sensorimotor polyneuropathy in patients with underlying malignant disease may sometimes be confused with the toxic effects of chemotherapy. Vincristine, a drug now much used for certain forms of cancer, may cause clinical manifestations similar to those of mixed sensorimotor polyneuropathy. Vinblastine sulfate is less likely to do so, but in high doses it also can bring about peripheral neuritis. The distinction between the drug effect and the possibility of spontaneous peripheral neuritis is not always an easy one.

Mononeuritis

In addition to the sensory and mixed polyneuritis forms associated with remote malignant lesions, mononeuritis has also been reported in association with an underlying neoplasm.[41] Patients with a wide variety of neoplasms had mononeuritis of one or another of the peripheral nerves, including the peroneal, radial, ulnar and lateral cutaneous nerve of the thigh. In none of these patients was there any indication of direct compression or invasion by tumor. It is conceivable that, like other patients with chronic diseases, patients with cancer are more likely to have compression neuropathy than are normal persons. Although this susceptibility may be the explanation for mononeuritis, the precise mechanism is not clear.

V. Muscle

Neuromyopathy

This is a confusing term and the condition to which it applies is sometimes classified as "polymyopathy." It is confusing because all the syndromes we have been describing are grouped under the general term "carcinomatous neuromyopathy." This semantic difficulty is unfortunate because neuromyopathy turns out to be the most common of all the neuromuscular syndromes associated with an occult neoplasm. It is characterized by symmetrical proximal muscle weakness and wasting of the muscles of the shoulder and pelvic girdles. It develops in subacute fashion and is usually associated with diminution or absence of deep tendon reflexes, although the ankle jerks are frequently preserved.[7,42]

The muscle weakness is probably not a result of the general cachexia of cancer, as it may occur in patients who are otherwise in good clinical condition. There is also no correlation between the occurrence of the muscular disorder and the amount of weight loss. The muscle weakness may precede the discovery of carcinoma by a considerable time. It has been estimated[43] that proximal muscle weakness developing in a male over age 50 has a 60 percent likelihood of being associated with a remote malignant lesion, while in women of the same age the likelihood is only 18 percent. Muscle biopsy and electrodiagnostic studies in such cases show primary muscle degeneration.

Our own experience indicates that this is a common form of neurologic change in patients with underlying malignant disease. Although it might be so subtle as to be overlooked on casual examination, it will be found fairly frequently in cancer patients if specific search is made. It occurs most commonly in patients with carcinoma of the lung but may be seen with other neoplasms as well. Steroid treatment has not been effective in alleviating the symptoms in severe cases, but striking remissions have occurred when the underlying neoplasm was treated. The specific method of treatment of the cancerous condition does not appear to be a significant factor in remission of neurological symptoms. A practical consideration with these patients is that they may have an abnormal sensitivity to muscle relaxants,[44] and for that reason it is important to recognize the syndrome before surgical treatment is undertaken.

Myasthenic Syndromes

Classical myasthenia gravis may be associated with a thymoma which not infrequently undergoes malignant degeneration. However, a more specific form of myasthenic syndrome associated with underlying malignant disease, particularly cancer of the lung, was described by Eaton and Lambert.[45] As they reported them, the clinical symptoms in this syndrome strongly suggested myasthenia gravis but electromyographic studies showed a defect in neuromuscular transmission different from that of the classic picture. The major clinical features that have been observed are weakness and easy fatigueability of proximal muscles, diminished deep tendon reflexes, and relatively poor response to neostigmine but pronounced sensitivity to tubocurarine. A fairly characteristic clinical observation in the patients with underlying malignant disease has been a delay in ability to perform a first contraction on ergographic examination. Normally in myasthenia gravis, when the patient squeezes an ergograph there is no delay in the first contraction. When the myasthenic syndrome is associated with an underlying malignant lesion, however, many patients show an appreciable delay in the development of a full contraction at the onset of maximal voluntary contraction.

It has been shown electrically that the principal defect in neuromuscular transmission in patients with myasthenic symptoms associated with cancer is a block of transmission in rested muscle but a decided enhancement of transmission in active muscle. These patients also respond less well than do those with classic myasthenia to the drugs usually used in treating myasthenia. Several of these patients have been reported to have had dramatic relief of the myasthenic syndrome following treatment of the underlying tumor.

In advanced stages of the disease the clinical characteristics of myasthenia gravis are so striking that they are seldom misinterpreted. However, early cases frequently present difficult diagnostic problems. Historically, it is not easy to distinguish the myasthenic syndrome associated with underlying malignant disease from the classic syndrome of myasthenia gravis, except that the latter is more likely to include bulbar symptoms. However, on examining patients with cancer-related myesthenia, one is struck by the difficulty they have in initiating a maximal voluntary contraction. A test to elicit the difference can be done easily by rolling a sphygmomanometer with the cuff partially inflated and asking the patient to squeeze the device on command, and then squeeze it repeatedly once a second. With the classical myasthenic patient, the first squeeze will be prompt and strong, and then after several contractions the strength will begin to diminish. The patient with a myasthenic syndrome and cancer will have a delay in the first maximal contraction, although from then on the pattern will be similar to that of the classic myasthenic. We have seen patients in whom the diagnosis of cancer of the lung was made from this simple office examination. Although bronchogenic carcinoma is most likely to produce the syndrome, other neoplasms are sometimes responsible.

Polymyositis

Semantic difficulty surrounds the term *polymyositis* also, for it intimates proximal muscle weakness although reflexes, unlike those in *neuromyopathy,* are usually relatively well preserved. Dermatomyositis is associated with an underlying neoplasm in approximately 15 percent of the cases.[46] However, when one excludes children with this condition, the incidence of cancer among adults over 40 with dermatomyositis may be much higher, perhaps as high as 50 percent.[47] The effect that treatment of the tumor has on the muscle and skin manifestations is variable, and evaluation of the effectiveness of such therapy is complicated by the fact that spontaneous remissions have been known to occur in this condition.[48] Steroids may also be of some value in the treatment of dermatomyositis and polymyositis.

VI. Mixed

As was previously noted, it is perhaps more common for patients to have a mixed variety of neurologic syndromes in association with underlying malignant disease than a pure form of any one kind. In fact the combination of two or more of these syndromes makes the likelihood of an underlying neoplasm even more likely.[49]

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MEDICAL STAFF CONFERENCE

The Clinical Spectrum of Renal Potassium Wasting

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Associate Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

Dr. Drew:* A 58-year-old woman was referred to the University of California Medical Center in June 1967 for evaluation of severe muscle weakness. For ten years before admission the patient had recurrent outbreak of purpuric spots and petechiae on the legs precipitated by exercise, Raynaud's phenomenon of the fingers on exposure to cold, dry mouth, dysphagia, and nocturia. She had numerous episodes of burning and redness of the eyes and used artificial tears for relief of a gritty sensation in her eyes. Laboratory studies showed a mild anemia, a broad-based elevation in serum gamma globulin, Bence Jones proteinuria, and normal bone marrow. During the two-year period before admission the patient developed increasing weakness of the lower limbs manifested by frequent falls and by difficulty in climbing stairs and rising from a seated position.

At the time of admission she was unable to stand or walk unsupported, because of muscle weakness. She was pale and appeared wasted. The blood pressure was 110/60 mm of mercury, the pulse 94 and regular. Physical findings included reddened conjunctivae, absence of lacrimation (Schirmer test) and salivation, cheilosis, a grade 2/6 systolic ejection murmur along the left sternal border, hepatomegaly, and large areas of brownish pigmentation interspersed with petechiae over the pretibia. On slit lamp examination, degenerative changes of the corneae and a moderately severe keratitis was noted. Muscle tone was generally poor, and the muscles of the buttocks and thighs were strikingly diminished in mass. There was no muscle tenderness. Tests of muscle strength revealed decided weakness of the pelvic and thigh muscles, moderate weakness of the calf muscles, and slight weakness of the shoulder girdle muscles. Sustained contraction consistently produced involuntary spasm and pain in some of the affected muscles. The remainder of the neurological examination revealed no abnormalities.

Significant laboratory findings were: hemoglobin 10.7 grams per 100 ml, white blood cell count 3,100 per cu mm, serum total protein 8.9 grams per 100 ml, serum sodium 138 mEq per liter, potassium 3.2 mEq per liter, chloride 115 mEq per liter, total carbon dioxide 13 mmoles per liter, creatinine 1.9 mg per 100 ml, blood urea nitrogen 18 mg per 100 ml, calcium 8.9 mg per 100 ml, phosphorus 2.3 mg per 100 ml, alkaline phos-

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*William L. Drew, M.D., Resident III, Department of Medicine.

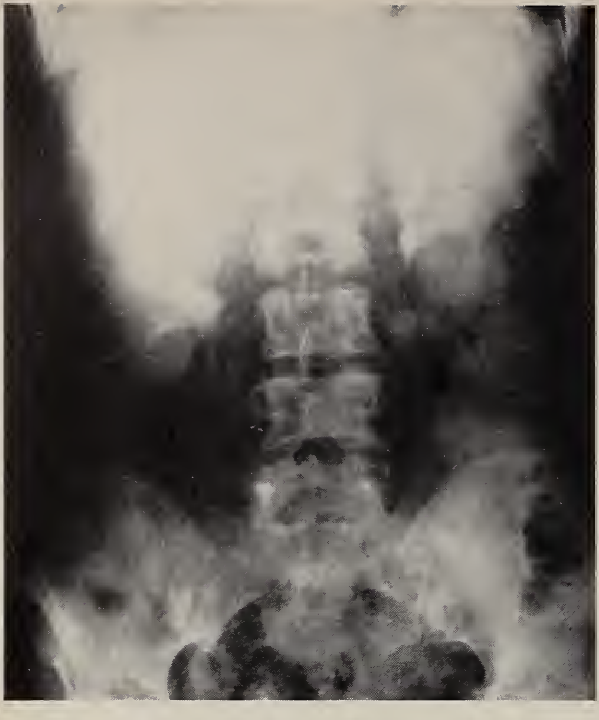

Figure 1.—Intravenous pyelogram showing small kidneys bilaterally and mild calyceal blunting.

phatase 17 Shinowara-Jones-Rinehart units (normal, 2 to 6 units). On paper electrophoresis 31 percent of the total serum protein migrated as gammaglobulin; the increase in gammaglobulin was broad-based and nonpeaked. The arterial pH was 7.25, and the plasma bicarbonate concentration was 12.5 mmoles per liter; the urine pH at the time was 6.5. The urine contained 400 mg protein per 24 hours and gave positive response to a heat test for Bence Jones protein; glucose was not present. Culture of the urine was negative.

Histologic sections of biopsy specimens of quadriceps muscle showed prominent perivascular infiltration with plasma cells, patchy subendomysial inflammatory infiltration, and atrophic muscle fibers. X-rays of bones showed diffuse demineralization, and excretory urograms showed contracted kidneys; nephrocalcinosis was not apparent.

Despite the presence of hypokalemia the patient excreted 45 to 60 mEq of potassium per day in the urine. When the arterial pH was 7.23 and the plasma bicarbonate concentration was 12.4 mmoles per liter, the urine pH was 6.68 and the rates of excretion of titratable acid (13.8 μEq per minute) and ammonium (13.0 μEq per minute) were distinctly subnormal. The clearance of inulin was 25 ml per minute. Maximal tubular reabsorption of bicarbonate, determined after acidosis and potassium depletion had been corrected for two months, was 1.6 mmoles per 100 ml of glomerular filtrate (normal, 2.6 to 2.9 mmoles per 100 ml); 24-hour urinary alpha-amino nitrogen was 250 mg (normal, 50 to 150 mg per 24 hours).

The clinical diagnosis was Sjögren's syndrome; chronic renal insufficiency associated with renal tubular acidosis, renal potassium wasting, and the Fanconi syndrome; and proximal myopathy.

Sustained correction of the patient's acidosis required the administration of 200 mmoles of bicarbonate daily. Correction of acidosis and maintenance of normokalemia with combined sodium and potassium bicarbonate was accompanied by striking improvement in the patient's muscle strength within three weeks. After three months of therapy she was able to rise unassisted from a seated position, walk unsupported for several blocks, and drive her automobile without difficulty, although some muscle weakness persisted.

DR. YOUKER:* An x-ray film of the chest showed slight ectasia of the descending aorta and considerable demineralization of the ribs; the heart and lung fields appeared normal. A skeletal survey, including films of the hands, showed generalized bony demineralization without evidence of pseudofractures or subperiosteal resorption. Films of the kidney after intravenous injection of Hypaque® demonstrated a reduction in renal size bilaterally and a minor degree of calyceal blunting (Figure 1).

DR. SMITH:† We have chosen this morning not to speak about Sjögren's syndrome *per se* — the systemic manifestations of this peculiar disorder — but to talk more specifically about the renal lesion and renal potassium wasting, renal tubular acidosis, and the concatenation of tubular defects seen in this patient, and to discuss more generally potassium wasting and renal disease. To lead the discussion we are calling upon Dr. Anthony Sebastian, who is a graduate of this school and formerly a member of our house staff. He is currently a Clinical and Research Fellow with Dr. Curtis Morris.

DR. SEBASTIAN:‡ Renal potassium wasting can be defined as the continued urinary excretion of more than 20 mEq of potassium per day in the presence of persisting hypokalemia. This definition is based on the observation that in normal subjects experimentally depleted of potassium, urinary potassium excretion decreases to less than 20 mEq per day when hypokalemia supervenes. These criteria identify renal potassium wasting in a variety of clinical conditions that include both primary renal disease (for example, renal tubular acidosis) and pathophysiological states of extrarenal origin (for example, alkalosis due to vomiting, primary aldosteronism) that result secondarily in urinary loss of potassium.

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†Lloyd H. Smith, Jr., M.D., Professor and Chairman, Department of Medicine.

‡Anthony Sebastian, M.D., Clinical and Research Fellow in Medicine.

Characteristics of Potassium Reabsorption and Excretion

The pathogenesis of renal potassium wasting in the conditions to be discussed this morning can best be understood in terms of the normal renal mechanisms of potassium reabsorption and excretion. Normally the clearance of potassium is only approximately 20 percent of the glomerular filtration rate, indicating that filtered potassium is largely reabsorbed. Micropuncture studies in the rat, dog, and monkey have shown that most of the filtered potassium is reabsorbed in the proximal portions of the nephron. The amount of potassium delivered to the distal convoluted tubule is less than 5 to 10 percent of the filtered load and remains essentially constant even when potassium excretion is greatly increased by potassium loading. Urinary excretion of potassium, therefore, under normal conditions and during potassium loading, is largely the result of net secretion of potassium in the distal nephron.

Potassium secretion occurs predominantly in the distal convoluted tubule; the secretory contribution of the collecting duct appears to be slight. Secretion of potassium by the distal tubule appears to be the net result of three major components of potassium transport: (1) active cellular uptake at the peritubular surface, (2) passive diffusion along a concentration gradient from cell to lumen, and (3) active reabsorption at the luminal surface.[1] Net secretion of potassium is critically dependent upon the delivery to the distal tubule of adequate amounts of sodium; conditions which decrease sodium delivery to the distal tubule result in a reduction in the rate of potassium secretion. Normally, the lumen of the distal tubule is electrically negative with respect to the peritubular fluid, and conditions which increase intraluminal negativity increase net potassium secretion. Intraluminal negativity and potassium secretion in the distal nephron are markedly increased by the presence of sodium salts of poorly reabsorbable anions (for example, phosphate, sulfate, and bicarbonate) under conditions in which sodium reabsorption in the distal tubule is augmented (for example, sodium depletion and hyperaldosteronism), and by the administration of carbonic anhydrase inhibitors. Hyperaldosteronism *per se,* in the absence of sodium depletion or increased amounts of poorly reabsorbable anion, also increases net potassium secretion in the distal convoluted tubule.

TABLE 1.—*The Clinical Spectrum of Renal Potassium Wasting*

I. Primary hypermineralocorticoidism
    A. Primary aldosteronism (adrenal tumor)
    B. Cushing's syndrome (bilateral adrenal hyperplasia, adrenal tumor, extra-adrenal malignancy)
    C. 17-Hydroxylation deficiency
II. Secondary hyperaldosteronism
    A. Hypertensive states
        1. Accelerated or malignant hypertension
        2. Renovascular hypertension
    B. Sodium-losing renal disease
    C. Juxtaglomerular hyperplasia (Bartter's syndrome)
III. Renal disease
    A. Renal tubular acidosis (classic RTA)
    B. Renal tubular acidosis associated with the Fanconi syndrome
    C. Pseudoaldosteronism
    D. Pyelonephritis?
IV. Miscellaneous conditions
    A. Acute or chronic metabolic alkalosis (e.g., vomiting, diuretic administration)
    B. Acute respiratory alkalosis (e.g., salicylate intoxication)
    C. Excessive ingestion of licorice
    D. Magnesium deficiency
    E. Acute monocytic and myelomonocytic leukemia

Clinical Spectrum of Renal Potassium Wasting

Table 1 summarizes the major clinical conditions in which hypokalemia and renal potassium wasting have been recognized. In the first two groups of disorders listed, renal potassium wasting apears to result from increased potassium ($K+$)-sodium ($Na+$) exchange in the distal tubule mediated primarily by the action of increased amounts of circulating endogenous mineralocorticoids. The designation "hypermineralocorticoidism," as opposed to "hyperaldosteronism," is used for the first group of disorders listed because in some of these conditions (including primary aldosteronism due to adrenal adenoma, Cushing's syndrome) adrenal secretion of desoxycorticosterone and corticosterone, each of which alone is capable of effecting renal potassium wasting, may be increased.

In most patients with Cushing's syndrome and in patients with the 17-hydroxylation deficiency syndromes, aldosterone secretion is in fact not increased.[2] In the conditions listed under "secondary hyperaldosteronism"—malignant and renovascular hypertension, sodium losing renal disease, and Bartter's syndrome—increased secretion of aldosterone appears to be mediated by continuous hyperactivity of the renin-angiotensin system.

A common pathophysiological state associated with renal potassium wasting is alkalosis (Table 1). Renal potassium wasting can occur both in metabolic and respiratory alkalosis. In the most common clinical states of metabolic alkalosis — alkalosis due to vomiting and diuretic-induced alkalosis — renal potassium wasting has been considered the result of accelerated $K+$-$Na+$ exchange in the distal nephron mediated in some way by concurrent chloride depletion and a continued stimulus to sodium reabsorption.[3] Chloride depletion and concomitant hypochloremia and reduced filtered load of chloride are presumably associated with a relative increase in the concentrations of poorly reabsorbable anions in the distal nephron which, in the presence of continued sodium reabsorption, increases intraluminal negativity and stimulates net potassium secretion. Because bicarbonate itself can act as a poorly reabsorbable anion, increased amounts of bicarbonate in the distal nephron may play a role in the stimulation of increased $K+$-$Na+$ exchange in metabolic alkalosis. Secondary hyperaldosteronism may also contribute to renal potassium wasting in clinical states of metabolic alkalosis.

Among the less commonly recognized causes of renal potassium wasting are excessive ingestion of licorice, magnesium deficiency, and acute monocytic and myelomonocytic leukemia associated with lysozymuria (Table 1). Licorice contains glycyrrhetinic acid, a substance which structurally resembles desoxycorticosterone and which, when ingested in excessive quantities, can produce a syndrome resembling hypermineralocortocoidism. Renal potassium wasting has been described in association with experimental magnesium deficiency in man. In recent years a number of patients have been reported in whom renal potassium wasting was associated with impaired renal conservation of magnesium[4]; the nature of the underlying disturbance in these cases has not been defined. The occurrence of renal potassium wasting in patients with acute leukemia has been reported so far only in abstract.[5]

Potassium Wasting Renal Disease

Renal disease *per se* is a relatively uncommon cause of renal potassium wasting (Table 1). Clinically, renal potassium wasting is recognized commonly in association with renal disease only in those renal tubular disorders that give rise to the syndrome of renal tubular acidosis. So-called pseudoaldosteronism (Table 1) is a rare disorder, described so far only in a single family in this country, in which a genetically transmitted abnormality of renal tubular function leads to sodium retention, potassium wasting, metabolic alkalosis, and hypertension.[6] The clinical presentation is similar to that of a primary mineralocorticoid excess syndrome, but the production rate and urinary excretion rate of known mineralocorticoids is reduced and the administration of the mineralocorticoid antagonist, spironolactactone, is ineffective in reducing urinary excretion of potassium. Successful treatment of these patients has been achieved with the use of triamterene, a natriuretic agent that inhibits renal tubular secretion of potassium.

Pyelonephritis has often been implicated as a cause of renal potassium wasting, but the evidence that pyelonephritis *per se* ever causes potassium wasting is unconvincing. Some cases, described before 1955, were subsequently discovered to have had aldosterone-secreting adrenal adenomas. In other cases renal potassium wasting appears to have been associated with underlying renal tubular acidosis.* To my knowledge, a systematic investigation of the ability of the pyelonephritic kidney to conserve potassium normally during potassium restriction has not been undertaken either in humans or in animals with experimental pyelonephritis. Since the medullary collecting duct is a site of significant net potassium reabsorption during potassium depletion, it would not be surprising if a disease of the renal medulla such as pyelonephritis was associated with impaired renal potassium conservation.

Renal Tubular Acidosis

Renal tubular acidosis (RTA) is a clinical syndrome characterized by minimal or no azotemia,

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*A recent case report by Gerstein and associates[7] perhaps best documents the concurrence of persisting renal potassium wasting and pyelonephritis unassociated with hyperaldosteronism, renal tubular acidosis, or other common cause of renal potassium wasting.

TABLE 2.—*The Clinical Spectrum of Classic Renal Tubular Acidosis*

- I. Primary
  - A. Sporadic
  - B. Genetically transmitted
- II. Genetically transmitted systemic disease
  - A. Ehlers-Danlos syndrome
  - B. Fabry's disease
  - C. Hereditary elliptocytosis
  - D. Galactosemia
  - E. Hereditary fructose intolerance
  - F. Sickle cell anemia?
- III. Hypergammaglobulinemic states
  - A. Idiopathic hypergammaglobulinemia
  - B. Hyperglobulinemic purpura
  - C. Sjögren's syndrome
  - D. Cryoglobulinemia
  - E. Chronic active ("lupoid") hepatitis
- IV. Medullary sponge kidney
- V. Hepatic cirrhosis
- VI. Primary hyperparathyroidism with nephrocalcinosis
- VII. Hyperthyroidism with nephrocalcinosis
- VIII. Drug induced
  - A. Amphotericin B
  - B. Vitamin D induced nephrocalcinosis
- IX. Pyelonephritis?

hyperchloremic acidosis, alkaline or minimally acid urine, bicarbonaturia, and reduced urinary excretion rates of titratable acid and ammonium. On the basis of certain physiological characteristics of the underlying renal acidification defect, two distinct subtypes of RTA can be recognized: (1) so-called classic RTA and (2) RTA associated with the Fanconi syndrome.[8]

In classic RTA bicarbonaturia persists and the urine pH remains inappropriately high even during severe degrees of acidosis; however, the magnitude of bicarbonaturia is a trivial fraction of the filtered load of bicarbonate. At normal plasma bicarbonate concentrations the fraction of the filtered load of bicarbonate excreted is usually less than 2 to 3 percent, a finding that excludes a marked impairment of bicarbonate reabsorption in the proximal nephron. The generally inferred operational mechanism of classic RTA is an inability of the distal nephron to maintain normally steep lumen-peritubular hydrogen ion (H+) gradients.[9]

On the other hand, in RTA associated with the Fanconi syndrome, the urine pH may decrease appropriately during severe or moderately severe degrees of acidosis, but bicarbonaturia occurs at subnormal plasma bicarbonate concentrations and the magnitude of bicarbonaturia increases progressively and strikingly as the plasma bicarbonate concentration is raised to normal levels.[8] At normal plasma bicarbonate concentrations the fraction of the filtered load of bicarbonate excreted varies from 15 to 40 percent, indicating that bicarbonate reabsorption in the proximal nephron is almost certainly impaired. An acidification defect of the proximal nephron accords with the finding in Fanconi's syndrome of generalized proximal tubular dysfunction — namely, aminoaciduria, glucosuria, and increased renal clearance of phosphate.

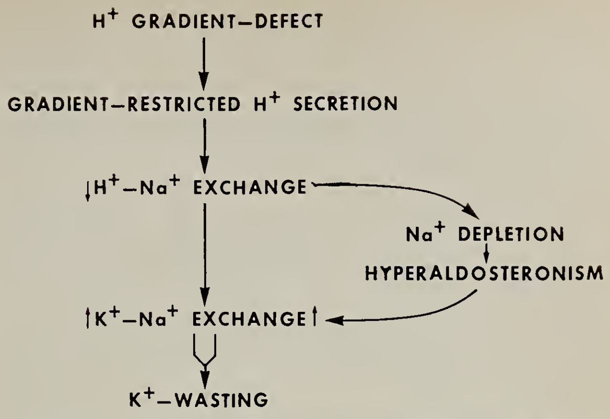

Chart 1. — Conventional pathogenetic scheme of renal potassium wasting in renal tubular acidosis.

Table 2 summarizes the clinical spectrum of classic RTA. Most cases occur sporadically and in women. The most frequently associated condition in the sporadic cases is hypergammaglobulinemia; including five cases of our own, we are aware of 39 instances in which apparently classic RTA has been associated with hypergammaglobulinemia. In several cases each, medullary sponge kidney, Ehlers-Danlos syndrome, and amphotericin B administration have been associated with apparently classic RTA. Some 20 families with RTA have been described. In many families the mode of inheritance of RTA appears to be autosomal dominant.

Renal potassium wasting in patients with RTA is generally considered a result of the underlying renal acidification defect[9,10,11] and not the result of an inherent defect in renal conservation of potassium. The mechanism of potassium wasting generally invoked is outlined in Chart 1. The inferred gradient limitation on H+ secretion in RTA presumably restricts H+ secretion in the distal nephron, thereby decreasing the maximally attainable rate of H+-Na+ exchange during acidosis. The rate of K+-Na+ exchange in the distal nephron is thought to increase reciprocally, either because potassium preempts a common K+/H+ secretory pathway or because of hyperaldosteronism secondary to continual urinary losses of so-

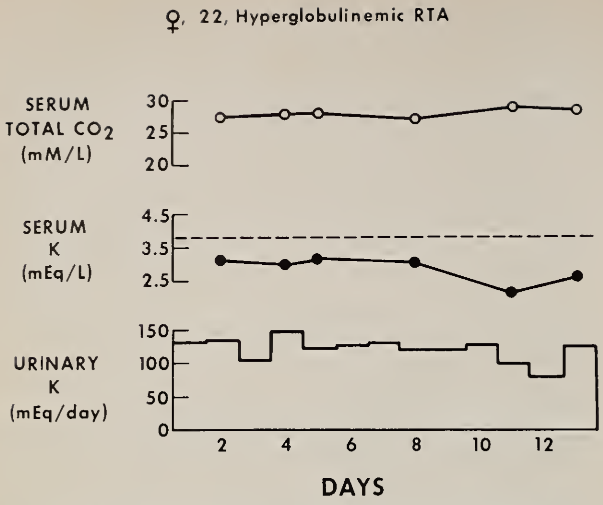

Chart 2.—Persisting renal potassium wasting during sustained correction of systemic acidosis with alkali therapy in a patient with classic renal tubular acidosis.

dium. The inferred role of a gradient limitation on H+ secretion in the pathogenesis of potassium wasting in RTA is based on the observation that correction of systemic acidosis by the administration of sodium bicarbonate ($NaHCO_3$) can reduce urinary potassium excretion and correct hypokalemia.[11] Increasing the plasma bicarbonate concentration, by increasing the filtered load of bicarbonate, increases urinary bicarbonate concentration and pH and presumably removes the gradient limitation on H+-Na+ exchange. H+-Na+ exchange increases; K+-Na+ exchange decreases. Correction of the sodium deficit removes the stimulus for hyperaldosteronism.

The traditional pathogenetic scheme fails to explain, however, the persistence of renal potassium wasting after correction of acidosis in some patients with classic RTA. One of our patients, a 22-year-old woman with hypergammaglobulinemia, required continued therapy with supplemental potassium despite sustained correction of metabolic acidosis and the absence of known causes of renal potassium wasting. Chart 2 documents the occurrence of persisting renal potassium wasting in this patient. The rate of excretion of urinary potassium was consistently greater than 100 mEq per day in the face of hypokalemia and sustained correction of acidosis. On repeated determinations during the two-week period shown in the figure, arterial pH, pCO_2, and plasma bicarbonate concentration were within the normal range. The urine pH was always greater than the minimally attainable pH during metabolic acidosis. Urinary aldosterone, 16 μg per day, was within normal limits. These findings fail to support the conventional view that renal potassium wasting results from a limitation on the rate of renal tubular H+-Na+ exchange.

In another patient with classic RTA, a 19-year-old woman with familial RTA, we investigated specifically whether removal of the gradient limitation *per se* on H+ secretion would result in cessation of renal potassium wasting. During metabolic acidosis and hypokalemia the patient excreted potassium at a rate of approximately 55 mEq per day, the urine pH was 6.1, and urinary aldosterone, 9.8 μg per day, was within normal limits. During gradual correction of the acidosis with $NaHCO_3$, the urine pH increased in stepwise fashion to values as high as 7.4, values at which renal tubular secretion of H+ is presumably no longer gradient limited. Yet renal potassium wasting was little affected, as indicated by the continued excretion of more than 40 mEq of potassium per day in the face of persisting hypokalemia. Although urinary potassium excretion decreased slightly as the acidosis was corrected, the absolute rate of potassium excretion remained inappropriately high in the presence of hypokalemia. Urinary aldosterone decreased to 6.4 μg per day as the acidosis was corrected. Renal potassium wasting in this patient, therefore, could not be attributed to an increased rate of potassium secretion reciprocal to gradient-limited H+ secretion or to hyperaldosteronism. Both this patient and the patient described previously required continued therapy with supplemental potassium to maintain normokalemia.

In four patients with seemingly classic RTA, Gill, Bell, and Bartter[11] recently demonstrated that the substitution of 100 mEq of $NaHCO_3$ for 100 mEq of sodium chloride in the diet resulted in (1) correction of systemic acidosis; (2) reduction of urinary sodium, potassium and aldosterone; and (3) sufficient positive potassium balance to correct hypokalemia. These workers interpreted their findings as supporting the traditional hypothesis that the inferred gradient limitation of H+-Na+ exchange in RTA underlies renal potassium wasting. The data reported, however, do not exclude a persisting defect in renal potassium conservation. Because the urinary excretion rates of potassium were not reported, it is not known whether, during the period of positive potassium balance, urinary potassium excretion decreased to appropriately low levels in the presence of hypokalemia. It is conceivable that, at the prevailing levels of potassium intake in these patients, sufficient positive potassium balance to correct hypokalemia resulted from only modest decrease in urinary potassium excretion. A mild, but nevertheless persistent, impairment in renal potassium conservation may be demonstrable in some patients with RTA only under conditions of low-normal or reduced potassium intake.

The demonstration in two patients with classic RTA that renal potassium wasting can persist in the absence of systemic acidosis, apparent gradient limitation on H+-Na+ exchange, hyperaldosteronism, or other known causes of renal potassium wasting raises the possibility of a primary defect in renal conservation of potassium in this disorder. The nature of the underlying renal "lesion" or "lesions" in RTA has not been established; some workers have speculated that increased permeability of the distal nephron to H+ might result in its excessive back-diffusion, thereby impairing urinary acidification. The same defect that precludes the establishment of appropriately high intraluminal H+ concentrations during acidosis could also preclude the establishment of appropriately low intraluminal K+ concentrations, irrespective of the state of systemic acid-base balance. A mild defect of this kind might become evident only during potassium restriction; a severe defect could result in renal potassium wasting despite normal potassium intake and sustained correction of metabolic acidosis.

An alternative explanation for the persistence of renal potassium wasting in our patients with classic RTA must be considered. It is possible that, despite the finding of normal urinary excretion rates of aldosterone, the prevailing secretion rates of aldosterone were, in fact, excessive for the degree of potassium depletion in these patients. In the presence of potassium depletion, the normal increase in aldosterone secretion and excretion that occurs in response to sodium depletion may be considerably blunted. If the finding of normal urinary excretion rates of aldosterone in the presence of hypokalemia represents, in fact, hyperaldosteronism in our patients, then two questions must be answered:

1. Could the prevailing presumably normal secretory rates of aldosterone mediate persisting renal potassium wasting?
2. What is the stimulus to hyperaldosteronism?

That normal levels of aldosterone can mediate persisting renal potassium wasting in the presence of hypokalemia is suggested by the observation that in some patients with aldosterone-secreting adrenal adenomas, aldosterone secretion may be within normal limits, yet hypokalemia and renal potassium wasting persist.[12] This finding suggests the possibility that in the presence of potassium depletion the renal tubule may be supersensitive to the action of aldosterone.

A possible stimulus to persisting hyperaldosteronism in patients with classic RTA is sodium depletion secondary to continued urinary loss of sodium. The possibility must be considered that renal sodium wasting might persist in some patients with classic RTA despite sustained correction of acidosis and removal of any gradient limitation on H+-Na+ exchange, perhaps as a consequence of a gradient limitation on sodium reabsorption *per se*.

The Fanconi Syndrome

In patients with RTA associated with the Fanconi syndrome, renal potassium wasting appears to occur invariably. No systematic studies have been reported which attempt to define the characteristics of the defect in renal potassium conservation in this disorder. In the past the pathogenesis of renal potassium wasting in Fanconi's syndrome was not considered separately from that in classic RTA. In many cases, however, renal potassium wasting cannot be attributed to the consequences of gradient limited H+-Na+ exchange because the ability of the kidney to maintain normally steep lumen-peritubular H+ gradients appears intact.[8]

Renal potassium wasting in patients with RTA and Fanconi's syndrome can occur in the absence of systemic acidosis or increased urinary excretion rates of aldosterone. We attempted to discontinue supplemental potassium therapy in a patient with RTA and Fanconi's syndrome associated with multiple myeloma. As the patient's supplements of potassium were gradually discontinued, severe hypokalemia recurred despite sustained correction of acidosis. Although urinary potassium excretion decreased in parallel with the decrease in potassium intake, the absolute rates of potassium excretion remained inappropriately high relative to the degree of hypokalemia. When the serum potassium concentration was as low as 2.6 mEq per 100 ml, urinary potassium excretion was still greater than 40 mEq per day. Urinary aldosterone, initially 9.4 μg per day, decreased to 3.2 μg per day during the course of the study. The urine pH remained consistently greater than the arterial pH. Accordingly, neither hyperaldosteronism nor a gradient limitation on H^+ secretion could be supported as underlying renal potassium wasting in this patient.

It has been stated that supplemental potassium should not be continuously required in patients with RTA associated with the Fanconi syndrome once systemic acidosis has been corrected. In our experience with approximately 12 patients, however, hypokalemia invariably persists or supervenes unless potassium supplements are continued, despite sustained correction of systemic acidosis. Since, whenever measured, urinary potassium excretion approximates potassium intake, it is likely that persisting hypokalemia is the result of continued urinary losses of potassium. We are not aware of any documentation that renal potassium wasting can be corrected in these patients by correction of acidosis with alkali therapy alone.

Dr. Smith: Thank you very much, Dr. Sebastian. I wonder if Dr. Earley has any comments about this patient or this problem.

Dr. Earley:* To what extent does the role of increased delivery of $NaHCO_3$ to the distal nephron in patients with impaired proximal reabsorption of bicarbonate influence potassium loss in the urine?

Dr. Sebastian: We have considered the possibility and are currently investigating the relationship between urinary potassium, sodium, and bicarbonate excretion in these patients. To the extent that sodium wasting occurs, secondary aldosteronism in some patients may also contribute to potassium wasting. The situation may be analogous to that in salt wasting nephritis in which the combination of increased sodium delivery to the distal nephron and secondary aldosteronism leads to marked renal potassium wasting.

Dr. Salmon:* Are conditions associated with hypergammaglobulinemia commonly associated with renal potassium wasting?

Dr. Sebastian: In all of the conditions in which classic RTA occurs in association with hypergammaglobulinemia, potassium wasting may occur. In a review of approximately 40 cases, hypokalemia was initially present in over 85 percent.

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AN EASIER POSITION FOR ANTERIOR ANASTOMOSIS

In colonic surgery, why do you do a 90-degree rotation of the mesenteric margin of the proximal segment when you do an anterior anastomosis?

"I've found that if you lay the sigmoid colon into the hollow of the pelvis it tends to fall on its left side and that it's easier to do the anastomosis in this manner. I believe that it probably decreases the amount of tension which the anastomosis is under. Certainly, it heals and functions just as well as if it were put in its correct anatomical position."

—William M. Mutch, Jr., M.D., San Francisco
Extracted from *Audio-Digest Surgery,* Vol. 15, No. 23, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

Medicine in Perspective

Historical Reflections on the Changing Concepts of Disease

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ONE OF THE MANY ASPECTS that makes the reading of Hippocratic medicine so superbly interesting is the fact that the ancient Greek medical writer had practically no medical terminology. Medical nomenclature developed slowly and gradually, in pace with the gradual development of medical knowledge; and so long as medical knowledge was restricted, a narrative, descriptive style was used to evoke a picture of a disease, where nowadays one word, a simple disease name, would suffice. From a literary point of view the Hippocratic method of medical writing was eminently more pleasing. But it was satisfactory also from a medical point of view, for many of the ancient descriptions were so succinct and detailed that they presented as graphic a picture of the disease under discussion as can now be found in the most modern medical textbook. This is perhaps best illustrated by the reading of one short excerpt. It deals with a disease whose name I need not mention, but which will be recognized by everyone in all its detail and ramification.

"In Thasus, early in spring. . . . Many had swellings beside the ears, either on one or both sides, in most cases without fever, and not necessitating confinement to bed; some, however, were a little heated. In all cases these swellings subsided without giving trouble, and none went on to suppuration as do those from other causes. In character they were flabby, large, diffuse, without inflammation or pain; in all cases they disappeared without a sign. These conditions occurred in youths, young men, and adults; mostly in such as took exercise in the wrestling schools and gymnasia; but they seldom attacked women. Many had dry coughs without expectoration; and hoarseness in speaking. Not long after, but in some cases a considerable time later, painful inflammation occurred in one or both testicles; fever in some cases, in others not. The condition was as a rule very troublesome. In other respects they had no illnesses requiring medical attention."[1]

This passage gives emphasis to a phenomenon which is of great importance to our subject: The disease in question, mumps, is so well observed that it need not be named. It was described more than 2,000 years ago. And yet, it might be a description of a mumps epidemic of today. The same is true for most other diseases given in the Hippocratic writings. From this we must conclude that while in the nearly twenty-five hundred intervening years since the days of Hippocrates some diseases may have undergone slight changes or permutations, most of them have existed in their present form since the beginning of history. Thus, what is unchanged is disease. What did change, however, is the way in which disease was looked upon.

This change is twofold: first, it refers to the pathological, physiological and etiological concepts and hence also to therapy. And second, it refers to the social aspect of disease in general and of individual diseases in particular.

The distinction which we now make between disease in general and individual disease or disease entities is a very important one. It did not come about automatically, nor early in the history of medicine but was the result of long experience and increasing sophistication in medical thought. Thus, while some individual diseases were known and recognized fairly early in the evolution of medicine, they were not looked upon as distinct entities but rather as manifestation of a state of disease

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This paper was based on a lecture delivered at the Hixon Hour, 17 March 1969, University of Kansas Medical Center, Kansas City, Kansas.

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that affected the human body *in toto*. This is, of course, particularly evident in primitive cultures, where all aspects of disease—etiology, pathology and therapy—were related to superhuman influences. Gods, evil spirits, demons did not send a sore throat or appendicitis or a broken leg; they sent disease, a state of illness which attacked the body in general, although it might be manifest in one particular spot only. Conversely, to treat disease, the exponents of primitive medicine, the shaman, or medicine man, did little for the affected part of the body, but rather tried to appease the powers that had sent the disease. In doing so they acted entirely logically—even if not altogether rationally from our point of view. They avoided the treatment of the disease itself and went straight to the root of the evil, namely, to assuage the wrath of the powers that had caused it. With the appeasement of the superhuman powers by prayers, incantations and sacrifices, the manifestation of their anger—that is, the disease itself—was bound to disappear.

The eventual divorce of medicine from superhuman connections was finally and clearly pronounced in the Hippocratic writings (fifth to fourth century B.C.) and finds succinct expression in the treatise on epilepsy, entitled:

"On the Sacred Disease"

> "It is this with regard to the disease called *Sacred:* it appears to me to be nowise more divine nor more sacred than other diseases, but has a natural cause from which it originates like other affections. Men regard its nature and cause as divine from ignorance and wonder, because it is not at all like to other diseases. And this notion of its divinity is kept up by their inability to comprehend it. But if it is reckoned divine because it is wonderful, instead of one there are many diseases which would be sacred; for, as I will show, there are others no less wonderful and prodigious, which nobody imagines to be sacred."[2]

It is difficult to appreciate fully the impact and importance of this statement. It removed disease from the hazy spheres of the heavens and brought it down to earth and into the realm of the physician's responsibility. The physician's every act now became important and it was up to him, and no longer to the deities, to treat and cure the patient.

Of course, the removal of the gods from the concept of disease necessitated the formation of new frameworks of thought for the cause and the cure of illness. Since it was no longer the deities whose pleasure maintained the harmony of the human body and whose displeasure caused disharmony and disease, other bases for harmony and disharmony had to be found. The first of these bases was known as humoral pathology; it was the theory of the harmony or disharmony of the four elementary substances, the four humors (yellow bile, black bile, phlegm, and blood). The preponderance of each of these led to either the choleric, melancholic, phlegmatic, or the sanguine personality type. Another theory of health and disease was that of the so-called solid pathology of the atoms, the solid minute particles whose harmony—that is, whose even distribution and free flow—maintained health and whose stagnation or plethora caused disease and death.

Thenceforth, the scholarly physicians of Greece and of the later Graeco-Roman period distinguished illnesses not so much by their location and manifestation as by their supposed cause, whether a preponderance or lack of one of the four humors or an exaggerated constriction or relaxation of the atoms. Translated into practice, this meant that the physicians who believed in the pathology of solids gave constricting or relaxing remedies as the case might require (following the maxim of *contraria contrariis*). Those who adhered to the concept of humoral pathology attempted to supplement the deficient humor by related foods or to combat the superabundant humor by foods with opposing properties. Together with these measures, however, which were directed to the theory of disease, the physicians also attempted relief of the symptoms which actually represented the individual illness.

The medical theorists in Greece, that is, those who saw the cause of disease in dyscrasia of humors or an imbalance of atoms, maintained their point of view well into the first centuries of our era, and, indeed, the humoral theory continued to persist until the rise of modern medicine. Not only for physical disease was humoral imbalance considered responsible, but also in the attitudes toward mental health and disease this theory played an important role. The melancholic person in whom black bile *(melas cholé)* predominated, the choleric who was full of yellow bile, the sanguine person and the phlegmatic became prototypes of personality and behavior—often found in the plays of Shakespeare—and have remained so ever since.

Disease as the Work of Witches

The spirit peculiar to the Middle Ages, however, re-introduced a concept of disease that was strongly reminiscent of primitive medical thinking. Again a punishing deity began to send disease to chastise humanity with epidemics of a vast variety and unsurpassed severity—particularly the Black Death, that is, the plague. And again mankind attempted appeasement of the offended deity by means of prayers, fasting and incantations. Thus once again the practice of medicine was shared by the priest. Of course, a great many of the medieval monks were trained in the practice of medicine, and they could give medical care, as well as spiritual. But it was largely the pure cleric, not the medically trained monk, who gave medieval medicine its superhuman stamp.

Perhaps the best example for this removal of all physical considerations from the realm of medicine can be found in a work that was actually composed during the Renaissance, but which is unsurpassed as a prototype of medieval reasoning. This work, the *Malleus Maleficarum*[4]—the "Witches' Hammer"—stemmed from the pen of two Dominican monks, Johann Sprenger and Heinrich Kraemer, who had been appointed Inquisitors of Northern Germany by Pope Innocent VIII. Fortified by a Papal Bull of 1484, these two men composed a work in which any mental and physical aberration from the norm was ascribed to deviltry, witchery and evil. The volume became the guidebook for the Inquisition and went through nearly 20 editions within two centuries. The latest edition (of 1928) rendered it into English.

The "Witches' Hammer" is divided into three parts. The first is devoted to the proof of the existence of witchcraft, the second presents "clinical reports" of the manifestation of the various types of witches, and the third deals with legal aspects of establishing and sentencing witchery. In the course of the Middle Ages the differentiation between the mentally sick, the witch and the heretic had become less and less sharply defined; and in the 13th century they were considered synonymous by most persons. Eventually, however, all diseases came into the realm of witchery. This can be illustrated by the following statement emanating from the pen of a member of the Inquisition.

"There is no part in our body that they [the witches] would not injure. Most of the time they make the human being possessed and thus they are left to the devils to be tortured with unheard of pains. They even get into carnal relations with them. . . . Unfortunately, the number of such witches is very great in every province; more than that, there is no locality too small for a witch to find. Yet Inquisitors and Judges who could avenge these open offenses against God and Nature are so few and far between. Man and beast die as a result of the evil of these women and no one thinks of the fact that these things are perpetrated by witches. Many suffer constantly of severest diseases and are not even aware that they are bewitched."

What, specifically, were the types of diseases that were removed from the responsibility of the physicians and put into the domain of religion? The "Witches' Hammer" enumerates them explicitly. The devil — or the witches — "have six ways of injuring humanity. And one is, to induce an evil love in a man for a woman, or in a woman for a man. The second is to plant hatred or jealousy in anyone. The third is to bewitch them so that a man cannot perform the genital act with a woman, or conversely a woman with a man; or by various means to procure an abortion. The fourth is to cause some disease in any of the human organs. The fifth, to take away life. The sixth, to deprive them of reason." *(Malleus Maleficarum,* p. 115)

It is clear that this listing comprises a very large part, if not most, of medicine, but some diseases are mentioned specifically for their demonic origin. Even the righteous monks felt that a special explanation was needed to make this plausible. The following is only one of many such examples.

And, ". . . although greater difficulty may be felt in believing that witches are able to cause leprosy or epilepsy, since these diseases generally arise from some long-standing physical predisposition or defect, nonetheless it has sometimes been found that even these have been caused by witchcraft." And then they give an example.

"For in the diocese of Basel, in the district of Alsace and Lorraine, a certain honest laborer spoke roughly to a certain quarrelsome woman, and she angrily threatened him that she would soon avenge herself on him. He took little notice of her; but on the same night he felt a pustule grow upon his neck, and he rubbed it a little, and found his whole face and neck puffed up and swollen, and a horrible form of leprosy appeared all over his body. He immediately went to his friends for advice, and told them of the woman's threat, and said that he would stake his life on the suspicion that this had been done to him by the magic art of that same witch. In short, the woman was taken, questioned, and confessed her crime.

> But when the judge asked her particularly about the reason for it, and how she had done it, she answered: 'When that man used abusive words to me, I was angry and went home; and my familiar [advisor, the Devil] began to ask the reason for my ill humor. I told him, and begged him to avenge me on the man. And he asked what I wanted him to do to him; and I answered that I wished he would always have a swollen face. And the devil went away and afflicted the man even beyond my asking; for I had not hoped that he would infect him with such sore leprosy.' And so the woman was burned."

This is only one of many similar examples.

Monks' Thoughts on Women

It is interesting that most of the victims of witchery were men, and that there were vastly more witches than wizards in the mental world of the Middle Ages and the two Inquisitors. While almost any known disease was described, and ascribed to witchery, the disturbances encountered most frequently relate to the reproductive organs. Sexual disorders, impotence and perversion, delusions of the loss of sexual organs occur with remarkable frequency. In view of the fact that the authors were monks and subordinate to the laws of celibacy, their preoccupation with these subjects is quite remarkable. Even more so, perhaps, is their attitude toward women, who, they felt, by their very nature, were disposed to enter into a compact with the devil. It almost appears as if they considered the state of femaleness a disease itself, when they exclaimed:

> "What else is woman but a foe to friendship, an unescapable punishment, a necessary evil, a natural temptation, a desirable calamity, a domestic danger, a delectable detriment, an evil of nature, painted with fair colours! Therefore, if it be a sin to divorce her when she ought to be kept, it is indeed a necessary torture; for either we commit adultery by divorcing her, or we must endure daily strife."

Thus, women, inferior by nature, lying, vicious and hopelessly impure, are naturally the most serviceable and most willing tool of the devil. The *Malleus* supports its misogynous contentions by way of another characteristic excursion into infantile philology—the alleged derivation of the Latin word for woman, *femina;* the word is supposed to come from *fe* and *minus* (without faith), the latter designating a defect in nature. Woman is also proved to be constitutionally inferior, because

> ". . . it should be noted that there was a defect in the formation of the first woman, since she was formed from a bent rib, that is, a rib of the breast, which is bent as it were in a contrary direction to a man. And since through this defect she is an imperfect animal, she always deceives."

The digression into the *Malleus Maleficarum* has served to illustrate the concept of disease as it was held by many of the clergy during the Middle Ages and even the Renaissance. While these men were probably altogether representative of medieval attitudes toward mental illness, there were a few other more enlightened healers, as well as a great many lay physicians who attended to man's *physical* diseases.

What were their concepts of disease? As was mentioned earlier, it was the humoral concept that persisted for more than a millennium. But the dyscrasia of humors was not too satisfactory an explanation for the rise and spread of medieval epidemics, such as leprosy, the plague, St. Anthony's fire (ergotism), the English sweating sickness and others of equally devastating nature. Nor was it sufficient to explain the existence of syphilis, the new scourge of the Renaissance.

A Tardy Understanding of Contagion

From our modern point of view it seems difficult to understand that the phenomenon of contagion was not recognized with the appearance of the first contagious disease. Yet, even as keen an observer as the author of the Hippocratic description of mumps failed to see why it was the men who congregated in gymnasia who contracted the disease while the women who stayed at home in relative isolation remained free from it. In the absence of a recognition of contagion, all sorts of other explanations were sought to account for the spread of disease. Foulness of the air, as in the case of malaria *(mal aria),* swampy exhalations in the form of miasma, artificially poisoned water and other imaginary causes gained firmly convinced adherents. In consequence, treatment was also geared to these hypothetical causes. Protection from the foul air was sought by means of perfumed sponges, windows were kept closed to keep out the miasma, and the pogroms against Jews (and others suspected of evil intentions) were held to prevent the alleged poisoning of wells.

Personal contact was feared only in the case of leprosy. Whether this was so because of the well-known biblical injunctions in Leviticus XIII, or because the disease in its medieval form was of a more contagious nature than we know it now, will never be known. Nor will we ever know whether the many outcasts diagnosed as lepers by non-medical authorities were actually sufferers from what later became more precisely defined as Hansen's disease.

The first truly modern biological concept entered medical thinking only with the earliest clear statement on the existence of contagion. This came into being amazingly late if we consider the clear disease pictures of the earlier days. After all, Hippocrates' description of mumps contained a clear picture of a contagious disease which was contracted by the men who gathered in the gymnasia but more rarely by the women who spent their days in the seclusion of their homes. The first clear statement of contagion was pronounced by Girolamo Fracastoro (1478-1553) of Verona, a true Renaissance personality who was at the same time a physician, a poet, a physicist, an astronomer and a pathologist. He is best known for his medical poem on syphilis, *Syphilis sive morbus gallicus* (Venice, 1530).[4] In this poem he coined the name of the disease and stressed its venereal cause. More important, however, is his treatise on contagion which was published in 1546. Here we find the first clear statement concerning the existence of microorganisms *(seminaria contagionum),* capable of reproduction in appropriate media. To be sure, Fracastoro did not think of these imperceptible particles whose existence he divined but could not prove, as living organisms *(contagia animata)* but we must consider that his work was done as early as 1530 and without the help of a microscope, in fact centuries before it was even invented. When we consider that Fracastoro worked solely on the basis of logical deduction, we must read in awed admiration his definition of contagion

> "If we allow ourselves to sketch a sort of tentative definition of contagion, we shall define it as: A certain precisely similar corruption which develops in the substance of a combination, passes from one thing to another, and is originally caused by infection of the imperceptible particles.
>
> "In what follows they are called [*seminaria contagionum,* seeds or] 'germs of contagion.'
>
> "There are, it seems, three fundamentally different types of contagion: the first infects by direct contact only; the second does the same but in addition, leaves fomes [fomites], and this contagion may spread by means of that fomes [fomites] — for instance, scabies, phthisis, bald spots, elephantiasis and the like. By fomes I mean clothes, wooden objects, and things of that sort, which though not themselves corrupted can, nevertheless, preserve the original germs of the contagion and infect by means of these; third, there is a kind of contagion which is transmitted not only by direct contact or by fomes as intermediary, but also infects at a distance; for example, pestilent fevers, phthisis, certain kinds of ophthalmia, exanthemata of the kind called variolae, and the like. These different contagions seem to obey a certain law."

It is not surprising that so revolutionary a doctrine failed to catch the imagination of Fracastoro's contemporaries. Indeed, it altogether failed to make a decisive impact on medicine until the 19th century, when the theory of microorganism could be substantiated by scientific measurements and apparatus.

Instead, the medical scientists of the centuries that followed the Renaissance persisted in the search for general laws by which to explain the phenomenon of health and disease. In keeping with the scientific movements of the 17th century, the interest of the physicians was drawn either toward the mathematical and physical discoveries of men such as Copernicus, Kepler, Galileo and Newton or toward the work of chemists such as Boyle, Willis and Mayow. Depending on the bent of their interest, they began to explain all bodily function and dysfunction either on mathematical or chemical principles and became known as Iatro- (from the Greek *iatros* = physician) physicists (also known as Iatromathematicians) or as Iatrochemists.

The "Sensitive Soul" Theory of Disease

As was to be expected, these two materialistic and mechanistic theories gave rise to a third, equally speculative but much more abstract, school of thought which began as "animism" and ended as "vitalism." It was conceived by Georg Ernst Stahl (1660-1734), a German who saw the "sensitive soul" as a source of all vital phenomena. Disease was a disturbance of the vital functions caused by the faulty activity of the soul. In fact, Stahl himself was a victim of this: he died in deep melancholia.

The idea of the soul as the source of life, as a regulator of physical function, and as a cause of pathological processes was immensely appealing to Stahl's contemporaries and successors. This idea can also be found in the writings of Barthez (1743-1806) of Montpellier, who coined the term "vital principle." It can also be found in the *élan vital,* by the philosopher Henri Bergson.

Even in the writings of Marie-Francois Xavier Bichat (1771-1802) this principle can be found. Bichat was the creator of descriptive anatomy and the founder of the field of histology. He examined the tissues of the body, unaided by the microscope, and defined 21 varieties of tissue. So far, he was a pure scientist, but then he concluded that each of the 21 tissues had its own specific vital property which made the tissue viable and gave it its specific character. Bichat, like the vitalists before him, regarded disease as an alteration of vital properties or principles. His definition of life, from which scientists still take an answer today, was "the sum of forces that resist death."

Perhaps it was not too astonishing that the somewhat mystic idea of vitalism persisted longest in Germany and had its most recent representative in the person of Hans Driesch in the early 20th century.

Vitalism, of course, is in conflict with science, with its search for measurable and demonstrable facts. Therefore, there is now no patience with or room for immeasurable or undemonstrable functions of the soul. Hence, the pendulum swings back to a more materialistic attitude toward the concept of disease. With the rise of chemistry and biochemistry, new concepts of disease came alive which are strongly remindful of the Iatrochemist of the 17th century who attempted to explain all physiology and pathology on chemical principles. And with the rise of physics and biophysics, we are again reminded of the Iatrophysicists of the 17th century.

However, there is one branch of medicine which is never able to dispense with the activities of the soul—and that is psychiatry. Stahl, the 18th century founder of vitalism, was also one of the early advocates of psychotherapy. He made striking observations of the effect of the mind upon the body, and his theory of the distraught psyche as a cause of disease contains more than a germ of Freud's teachings.

But even this sketchy outline of the history of the concepts of disease must make it evident that concepts rarely persist too long and that none of them ever remain unchallenged. Thus, even psychiatry, which deals with the psyche, the soul itself, is not left unshaken in its adherence to vitalist thought. Recent events in drug therapy have even brought the study of the treatment of the soul into the realm of the biochemist.

As an historian, I cannot project the history of the future. As a scholar, I cannot even venture to guess what concepts of disease are yet to arise. It is certain, however, that even our increasing knowledge of individual disease and our recognition of disease entities which have been unrecognized during the first two millennia of medical history, will not end the quest for the ultimate concepts of disease.

There will always be a search for an answer to all ills—perhaps in the hope that one day one school of thought will find the one true concept that has power over all disease.

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A State Medical Association on the Move

Part II: Pioneers in Planning

Robert L. Thomas, *Executive Director, California Medical Association*

It has been said that planning builds a bridge between where an organization is and where it wants to go. Planning can make things happen that otherwise might not occur. It brings objectives into focus. Within the California Medical Association structure, planning has helped to unify activities of various commissions and committees.

The Bureau of Research and Planning

One of the first visible affirmations of CMA's belief in planning was the establishment of its unique Bureau of Research and Planning in 1958. When the formation of the Bureau of Research and Planning was authorized by the CMA House of Delegates, one of its principal objectives was seen as the development and initiation of long range plans and programs. Ever since the first meeting, the bureau has been looking far into the future with proposed studies of medical education and health manpower; organization and distribution of medical services; philosophy and demands of labor in regard to medical care, and medicine's role in government medical care programs.

At the time the bureau was formed, there was no other single organization or agency—government or private—sponsoring research of any magnitude directed at seeking factual unbiased information which could help the CMA reach sound conclusions and develop constructive, farsighted policies. The bureau has filled this vital need by laying a firm foundation of research for more purposeful planning by the CMA.

In the ten years since it was established, the bureau's research and studies have been used by all divisions of the CMA to guide them in planning future activities and policies. A recently completed study on professional liability coverage in California assisted the CMA in formulating recently adopted legislative recommendations dealing with this complex problem; the *Reference Book on Selected Health Manpower Data (Revised—1968)* provided definitive information on health manpower in California that will be of the utmost importance, not only to the CMA but to all the allied professions, in anticipating our future needs; a comprehensive, statewide survey by the CMA among physicians concerning their attitudes toward workmen's compensation formed the solid basis for testimony presented by the CMA to the "blue ribbon" Workmen's Compensation Study Commission, the Division of Industrial Accidents, and the State Legislature and ultimately resulted in beneficial changes in the program; a survey on disaster and emergency medical care facilities in the state now under way will be of invaluable assistance in planning for adequate medical coverage in case of disaster. The results of the survey on continuing medical education will provide important guides in planning the most effective course to be taken by medical education for the practicing physician.

The bureau's efforts and accomplishments received national recognition last October when the

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The first article, *A State Medical Association on the Move*, on the progress of the California Medical Association, appeared in California Medicine, 108:464-468, June 1968.

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National Association of Blue Shield Plans presented the Bureau of Research and Planning with its Norman A. Welch award for "the most scholarly and meritorious contribution to the literature of medical economics." The award to the CMA was the first ever made to a medical association in the United States.

The Committee on Organizational Review and Planning

With the growth in size, activities and influence of the CMA during the past decade, it seemed imperative that the structure and functions of the CMA as they relate to its goals be reviewed and defined. In 1966, the Committee on Organizational Review and Planning (CORP) was created as a special committee of the Council to meet this need. The committee was further instructed:

- To review and analyze problems in whose solutions CMA should lead and participate;
- To review the structural organization of the CMA; and
- To plan for and propose changes in CMA organizational structure to improve its overall functioning.

During the year just past, CORP divided its attention between the review of the structural organization of CMA and the analysis of problems crucial to the CMA. Three of these critical problems were examined as a result of CORP's critique and commentary on the Report of the National Advisory Commission on Health Manpower: (1) Physician manpower in California; (2) organization and delivery of health care services, and (3) peer review. Further study to aid in planning will be carried out during the coming year by the appropriate CMA committees.

During the next year, CORP will continue its analysis of CMA's organization in relation to the problems, social changes and challenges that confront it.

The Committee on the Role Of Medicine in Society

By presenting realistic and frank discussion of the issues that confront medicine today, the Committee on the Role of Medicine in Society seeks to help shape the role of the physician and medical practice in the years immediately ahead. Four progress reports have been published by the committee since it was established. Its most recent report, "A Role for Medicine in a New Era of Health Care," offers recommendations for long-range planning to insure that the medical profession will retain its position of leadership in the organization and delivery of health care. This and the other reports of this committee have received nationwide attention.

In a current project, aimed at an important (but sometimes neglected) segment of future medicine, the committee has begun a study of the attitudes of medical students toward their chosen profession. The study will be repeated twice during the next seven years to investigate how these attitudes change during a seven-year period, and will be used to further determine the course to be charted for medicine in California.

CMERF and Comprehensive Health Planning

Through the California Medical Education and Research Foundation (CMERF), the California Medical Association has sponsored two (and is planning a third) national regional conferences on comprehensive health planning. The first Western Regional Conference on Future Directions and Decisions in Medical Care, was planned some time before Congress enacted P.L. 89-749 (Comprehensive Health Planning). The idea was conceived almost two years earlier in recognition of a need to explore some of the problems and issues confronting the medical profession. The passage of this legislation, however, brought into focus some of the immediate and long-range issues which the organized medical profession must face if it is to deal realistically with the problems ahead. At the first conference — the "Chandler Conference" because it was held at Chandler, Arizona — 14 states were represented by more than 200 physicians. CMA Past President John G. Morrison said, "It is one of the most challenging opportunities ever presented to the health care professions to plan for and to provide comprehensive health care services to the public."

In July, 1968, CMERF sponsored a two-day conference on the "Planning Process: Physician-Consumer Involvement in Comprehensive Health Planning." More than 150 program participants, a cross-section of providers, consumers, planners and private and public agencies in California, heard presentations from an expert panel of persons knowledgeable in several fields.

A second Chandler conference on comprehensive health planning is being projected for this fall.

Again, the primary objective will be to bring together leaders of medicine in the western United States to create an "awareness of some of the challenges, responsibilities and objectives confronting the medical and allied health professions on all community levels." It is certain that ideas given impetus there will play a large part in shaping the changes in medicine that are taking place now and that are yet to come. These CMERF-sponsored planning conferences have been an important stimulus to planning both within and outside of CMA.

Continuing Medical Education

In March 1967 the CMA Committee on Continuing Medical Education held a landmark conference to "define and delineate future policy and courses of implementing action for continuing medical education in California." The success of this "planning and goals" conference laid the foundation for a second, similar conference which was held in March of this year.

Discussion at the first conference focused in four specific areas: (1) The role of hospitals in continuing education; (2) an evaluation of continuing medical education and its effect upon the quality of care rendered by physicians; (3) how to motivate physicians toward greater participation in continuing medical education, and (4) accreditation or approval of postgraduate programs. One of the direct results of the first conference has been a census by the Bureau of Research and Planning to determine who attends courses, where the participants come from and what courses they attend. The results will be valuable in planning future postgraduate courses.

The 1969 Planning and Goals Conference was called in order to evaluate progress in implementing recommendations made at the first conference, to assess present patterns and effectiveness of continuing medical education in California, and to establish goals for the next two years.

These two conferences have been hailed as pacesetters in the field of continuing medical education for physicians. In applauding the leadership of the CMA in sponsoring these conferences, an editorial in the August 7, 1967, *Journal* of the AMA said: "This activity by a state medical association is encouraging indeed. It demonstrates that leadership in maintaining professional competence can be assumed by the profession itself. In the best interests of the profession, most would agree that this is exactly where it belongs. Hopefully, more state medical associations will initiate similar programs."

Council Planning Retreats

Since the Council of the CMA is the group responsible for implementing policy set by the House of Delegates, and for dealing with the myriad of interim problems that arise between annual meetings, Council members have felt that they too need time for thoughtful, creative planning.

To escape to an atmosphere of relative seclusion away from the month-to-month pressures of guiding an organization of the complexity and scope of the CMA, the Council held a Council planning retreat last fall.

Among other topics, the councilors discussed how they could best plan to meet CMA responsibilities in five major areas: peer review, intraprofessional relationships (including component societies, AMA and specialty societies), government relations, membership services, and public involvement.

Councilors were pleased by the results of their retreat, and it is scheduled to become an annual event on the Council calendar.

The "planning retreat" idea also has taken hold in component societies. The medical leadership of eight of California's 40 county medical associations held separate weekend retreats during the past year to discuss a variety of topics relating to local challenges.

Objectives and Goals

"There is much concern . . . over the need for goals," Charles L. Hughes, Ph.D., wrote in his book, *Goal Setting,* which the Committee on Organizational Review and Planning used as a guide. "Too often, however, we find lots of activity but little concern for where it is taking us," Hughes continued.

With this warning firmly in mind, your California Medical Association is moving toward a future it is helping to plan, with programs that not only will fill future needs, but even today are shaping the future itself.

For the past three years the CMA Council has developed and adopted an annual statement of objectives for the Association—in an attempt to state in more precise terms CMA's constitutional purpose: "To promote the science and art of medicine, the protection of public health and the betterment of the medical profession." While the broad objectives adopted by the Council and presented to the House of Delegates last March do not appear to differ substantially from those adopted in 1967 and 1968, there is in fact a vitally important difference. Each of the eleven 1969 objectives was further refined in terms of specific goals to be accomplished during the year. At its retreat next October, and again at the 1970 Annual Session, the Council will be able to measure the accomplishments of the various CMA commissions and committees against the specific goals.

These goals (see appendix) are giving form and substance to CMA activities now, and the broad objectives keep us unified, aiming together toward one common ambition—better medical care for all the people through better planning.

APPENDIX

1969-70 CMA OBJECTIVES AND GOALS

OBJECTIVE 1. Assure the citizens of California that the medical care rendered to them is of high quality.

Specific Goals for 1969-70 include:

A. Expand the CMA Medical Staff Survey concept to include all hospitals in the state (public and private).

B. Expand the Medical Staff Survey concept to include extended care facilities.

C. Work toward making CMA Medical Staff Survey approval a prerequisite for payment by third parties (for both government and non-government programs).

D. Assure that each county medical society has a functioning committee to survey the practice of medicine within the county, including a survey of samples of claims, either before or after they have been processed for payment by various insurance and prepayment organizations.

OBJECTIVE 2. Demonstrate to the citizens of California that their physicians possess the most modern medical knowledge.

Specific Goals for 1969-70 include:

A. Establish and make available to all physicians practicing in California the administrative mechanisms to collect, codify and certify participation in accredited postgraduate instruction.

B. Develop and implement method of accreditation of postgraduate efforts by physicians.

C. Issue mark of recognition to physicians fulfilling specified postgraduate education requirements, in cooperation with the AMA.

D. Develop criteria for judging whether a physician is fulfilling his responsibilities for postgraduate education.

E. CMA should try to stimulate development of methods for self-testing of physicians' knowledge (results could be used in lieu of evidence of attendance at courses).

OBJECTIVE 3. Improve emergency medical care services throughout the state.

(The Committee on Emergency Medical Care will bring to the Council recommendations from the Emergency Medical Care Survey of over 400 emergency facilities throughout the state. The Council will develop specific goals from these recommendations.)

OBJECTIVE 4. Continue efforts to keep the cost of health care at a reasonable level.

Specific Goals for 1969-70 include:

A. Work with the California Hospital Association and individual hospitals (through medical staffs and physicians on hospital boards) to increase efficiency in hospitals in areas of direct physician involvement (e.g., admissions, length of stay, etc.).

B. Educate physicians regarding their role and responsibility in keeping health care costs to a minimum.

OBJECTIVE 5. Intensify public involvement by the medical profession at all levels, with special emphasis on community involvement as paramount.

Specific Goals for 1969-70 include:

A. Identify organized medicine as a participant, with other groups, in solution of social problems in depressed areas.

B. Participate in pilot programs to alleviate specific disease entities in poverty pockets.

C. Develop a position paper on the role and function of a county medical society in multiphasic screening.

OBJECTIVE 6. Continue to make strides in alleviating the drug abuse problem among California's youth.

Specific Goals for 1969-70 include:

A. Participate in a public education campaign in cooperation with the Governor's office, the Public Relations Institute, and the Newspaper Publishers' Association.

B. Authorize the publication of the CMA fact sheet "Damaging Effect of Drug Abuse" as a pamphlet jointly sponsored by the PTA, the California Interagency Council on Drug Abuse and printed by the Department of the Youth Authority for statewide distribution.

C. Continue survey of county medical society activities as well as community programs around the state and in the school districts to determine what factors bring about an effective program of drug abuse education and prevention.

D. Communicate with county medical societies, individual physicians, parent groups and other organizations to extend consultation and aid in drug abuse education and control.

E. Lead in the formation of the California Interagency Council on Drug Abuse in a five-pronged attack on the drug abuse problem by task forces on: Administration of Justice, Education, Legislation and Government, Research, Treatment.

OBJECTIVE 7. Work to alleviate the health manpower problem in California, with particular attention to distribution of physicians in rural areas.

Specific Goals for 1969-70 include:

A. With other organizations, conduct recruitment drives in health careers.

B. Determine the extent of the need for additional physicians in rural areas and develop recommendations based on these findings.

C. Complete an analysis of the role of the "physician's assistant," (including a study of licensure requirements and professional liability problems involved).

D. Work with the Health Manpower Council to determine the extent of unmet needs for outpatient paramedical personnel.

OBJECTIVE 8. Devote effort to implementing the Medi-Cal program so that it will bring benefit of medical care with dignity to the indigent population without harm to any other segment of the population.

Specific Goals for 1969-70 include:

A. Take greater responsibility at the CMA level, for insuring that abuses of the program are kept to a minimum — in all areas of the state.

B. Work toward elimination of the concept of the "60th Percentile" in view of its inconsistency with the original intent of the law and its adverse effect on the numbers of physicians participating in the program (mainstream care).

C. Continue to pursue CMA policy to insure that appropriate investigative and disciplinary authority be granted to Medicine in cases of Medi-Cal abuse.

OBJECTIVE 9. Delineate the relationship of the hospital to the practice of medicine.

Specific Goals for 1969-70 include:

A. Promote continuing medical education in the hospital, (e.g., education aspects of medical staff committee functions, teaching and research institutions, effective utilization review, and the physician as a leader of the medical care team).

B. Participate in governing boards and administration liaison (e. g., involvement in hospital planning, design and management, common problems of malpractice, computerization, and community health services).

C. Develop and implement innovative extensions for the use of the traditional short-term acute general hospital, (e. g., expanding the spectrum of progressive patient care, evaluating special treatment units, and discussing the relationships of physicians' offices to the hospital seven-day work week).

OBJECTIVE 10. Make every effort to bring all California physicians into participation and support of CMA.

Specific Goals for 1969-70 include:

A. Give special attention to younger physicians by:
   1. Urging county medical societies to utilize and publicize affiliate membership for residents and interns.
   2. Developing communications specifically designed for younger physicians.
   3. Involving younger physicians to a greater extent in CMA and county society activities.
   4. Establishing a means of communications for the young doctor to make his voice heard in decisions of the CMA.

B. Invite specialty society presidents to CMA Council meetings and their executive secretaries to meetings of the Medical Executive Conference.

C. Actively involve organizations representing minority physicians in the work of CMA (for example, by inviting members to Council meetings and to county medical society board meetings).

D. Initiate an attitude study to determine to what extent CMA policy is truly representative of and understood by physicians throughout the state, and develop recommendations based on the study.

E. Unify the profession further by fully implementing the concept of the Scientific Board, by setting up an interspecialty conference with responsibility, authority and a budget, and by continuing to advance the advisory panels.

F. Encourage each county medical society to evaluate itself in terms of its potential for attracting new members.

OBJECTIVE 11. Develop and implement solutions to the professional liability problems facing California's physicians.

Specific Goals for 1969-70 include:

A. Continue, with CHA, to study the concept of arbitration and evaluate the present provisions for arbitration which are utilized by some prepaid medical service organizations.

B. Initiate a pilot study regarding the advisability of developing a scientific method of determining ways in which the size of malpractice awards might more reasonably and uniformly relate to the injury incurred.

C. Seek passage of legislation which would:
   1. Effect modification of interpretations of the doctrine of "res ipsa loquitur" and place a reasonable ceiling on malpractice damages.
   2. Place some reasonable limitation upon the "statute of limitations."
   3. Require the filing of a cost bond.
   4. Introduce the concept of a reversionary trust relative to longevity personal injury awards.

D. Repeat the successful "California Invitational" preventive malpractice workshops and develop and distribute suggested guidelines resulting from the workshops.

Government and Medicine

Medical Corporations–Some Observations

Howard Hassard, *Legal Counsel, California Medical Association*

Professional corporations can now be formed in 39 states, including California. It has been possible for a professional corporation to practice medicine in California since April 10, when regulations adopted by the Board of Medical Examiners became effective. Earlier this year, the formation of law corporations was authorized by the State Bar. Dental corporations are the most recent addition to this list.

The flood of applications which proponents of incorporation predicted has not materialized. The first step in incorporation is the filing of articles with the Secretary of State. As of May 1, less than 200 sets of articles had been submitted. More than half were returned unfiled, because of defects in draftsmanship or failure to comply with legal requisites.

The major reason professionals have not acted to incorporate is uncertainty as to the tax status of professional corporations. The Internal Revenue Service (IRS) has been an implacable opponent. Because the decision of a federal court in one part of the country does not necessarily bind courts in other parts of the country, the IRS has not been forced to abandon its opposition in spite of the fact that it has lost every case tried to date contesting the right of a professional corporation to corporate tax treatment. A significant blow was dealt the IRS on May 1, when the U.S. Court of Appeals for the 6th Circuit, in the case of *O'Neill v. U.S.*, followed other federal courts in ruling that IRS regulations treating professional corporations as a partnership for tax purposes are invalid.

The decision in the O'Neill case has prompted many inquiries, asking whether incorporation is now appropriate. The answer must be that some physicians may be well-advised to consider incorporation. However, caution and restraint are still very much in order. Even if IRS is compelled to recognize that professional corporations are entitled to corporate tax treatment, there are a host of pitfalls. It should be anticipated that the Internal Revenue Service will subject professional corporations to the closest scrutiny, and the defeat of IRS on this basic issue will not help the hapless professional who runs afoul of other rules of tax law.

Furthermore, there are practical problems which can be overlooked all too easily.

The "collapsible corporation*" problem, the Section 531 penalty (27.5 percent to 38.5 percent) on accumulations, the possibility of "personal holding company*" treatment and a consequent 70 percent extra tax, are amongst matters to be discussed with a knowledgeable specialist. The fact that presently available spendable income must be reduced to take full advantage of the corporate device must be appreciated. Many professionals will discover that incorporation would actually reduce both earnings and savings which might be realized without incorporation. This fact will become apparent only after competent analysis of the individual situation.

It is possible that the IRS may be forced to recognize properly formed professional corporations within the near future. It cannot be assumed that

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*These terms are used in tax regulations to identify certain kinds of entities that are sometimes set up to qualify for a selected status under tax laws.

this recognition will extend to the one-man or even to the two-man corporation. Recognition will not avoid other tax problems, including some which will be peculiar to professional corporations. The professional who is conservative in his approach may realize benefits (as the result of the sad experience of more eager contemporaries) which will outweigh any disadvantages caused by delay. In any event, the risks must be understood. We suspect that some of those who have rushed to incorporate (perhaps including some of the 38 law firms incorporated as of May 13) have not given due consideration to the disadvantages. Those who ignore the disadvantages, or who fail to consider their individual situation and needs, can expect disappointment. However, we would be remiss if we did not suggest that perhaps relatively few physicians are in a situation which justifies incorporation now, and knowledgeable advice is essential before this step is taken.

Correction:

PAY ROLL DEDUCTION FOR SOCIAL SECURITY

In the article "Physicians as Employers," pages 423-426, May 1969, an error was made in a statement regarding the amount an employer is required to withhold from an employee's pay under the Federal Insurance Contribution Act (Social Security). The sentence in question, appearing in the second paragraph of the first column on page 424, said that "as it stood at the beginning of 1969, an employer must withhold 4.9 percent of the wages of an employee that do not exceed $6,600 a year."

It should have said " . . . an employer must withhold 4.8 percent of the wages of an employee that do not exceed $7,800 a year."

Medical Schools of California

Loma Linda University School of Medicine

THE LOMA LINDA UNIVERSITY SCHOOL OF MEDICINE, which is closely affiliated with the Seventh-day Adventist Church, was originally chartered as the College of Medical Evangelists in 1909 and graduated its first class in 1914. The rural location at Loma Linda, about fifty-five miles east of Los Angeles near San Bernardino, developed as a basic science campus, and opportunities for clinical teaching were sought in urban Los Angeles.

A long and excellent affiliative teaching relationship was realized between the School of Medicine and the Los Angeles County General Hospital. In addition, the clinical program was significantly augmented by the building of the White Memorial Hospital and Clinic conveniently near the County Hospital. Accordingly, the medical school developed in a two campus form: the two basic science years in Loma Linda and the two clinical years in Los Angeles.

In 1961 the institution's name was changed to Loma Linda University to reflect its wider interests and involvements. The University now includes in addition to the original school of medicine, schools of dentistry, nursing, health-related professions, public health, education, and the graduate school. The university's College of Arts and Sciences is located on its Riverside campus. The very prominent health science related emphasis is a deliberate feature of the University's program.

With the passage of time it became increasingly clear that the two-campus situation resulting in the separation of the basic and clinical science instructional areas was inhibiting the long-range growth and development of the medical school. Consequently, in 1962 the decision was reached to move the clinical departments and their teaching activities from Los Angeles to the Loma Linda campus. This decision made long-range planning possible with respect to curriculum, faculty development, and the construction of seriously needed physical facilities. One can readily imagine the serious problems involved in the transfer of the clinical portion of a medical school from one area to another, including the establishment of new clinical facilities; and this extensive transfer certainly could not have been accomplished without the wholehearted cooperation of the trustees, faculty and student body. In addition, special thanks are due the Los Angeles County General Hospital and the School of Medicine of the University of Southern California for their strong understanding support during this critical period.

The complete transfer of the clinical teaching program to the Loma Linda campus, including the planning and construction of a new 510-bed university hospital and medical center, was accomplished by 1967. This medical complex, which became functional in July 1967, now constitutes the heart of the clinical teaching program. This unit includes outpatient facilities, departmental areas for the clinical faculty, and research laboratories.

The now united medical school is pleased to be located in the rapidly growing San Bernardino-Riverside area where valuable teaching affiliations have been established with local hospitals. The most significant of these is the affiliation with the Riverside County General Hospital involving all major clinical teaching disciplines. Patton State Hospital has proved to be an outstanding source of support in psychiatry. Important teaching relationships are being developed with the Kaiser

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Foundation Hospital. Limited but very helpful teaching opportunities have been provided by the March Air Force Base Hospital and the San Bernardino County General Hospital, and discussions are in process with other nearby hospital units.

Extensive study of the curriculum has been in process during the past four years with the hope that revisions could be made that would help to realize more fully the educational objectives of the school. These objectives include providing the student with an opportunity to build a sound foundation of basic medical knowledge and a sense of obligation to continue the learning process throughout his professional life; to develop investigative curiosity and problem-solving approaches to medical problems; to be guided in the development of a balanced set of values as revealed in intellectual, ethical and spiritual attitudes. It is hoped that the student will recognize in medicine a high calling and will be unselfishly motivated toward mankind and his problems.

The curriculum is largely based on an interdisciplinary approach during the first two years in which basic and clinical scientists together present the so-called "core of medical knowledge" through lectures, seminars, laboratory experiences, demonstrations and limited appropriate clinical activities. Clinical activity in psychiatry and behavioral science is also a part of the first and second years' curriculum. The third year (12 months) is devoted to an intensive, highly patient-oriented clinical clerkship experience, with the student serving as "assistant intern." The clinical time is shared by internal medicine, surgery, pediatrics, gynecology and obstetrics, and psychiatry. The fourth or senior year is on a guided elective basis, providing the student with an opportunity to explore an area of choice in considerable depth, to contact a broader range of interests, or perhaps to pursue a significant research problem. It is hoped that this curricular approach will provide a reasonable balance of disciplined learning and flexibility to meet the challenges of medicine as they appear.

The school at present admits approximately a hundred students to its freshman class and looks forward to a modest increase in this number in recognition of the medical manpower needs of the nation and the world. Expansion of the basic science teaching facilities will be necessary, however, before any significant increase in enrollment can be achieved.

The School of Medicine now has more than 4,000 alumni. Although a significant number of these physicians reside in California and contribute to meeting local medical needs, the alumni distribution in general is extremely cosmopolitan with respect to the United States and abroad. The school has always had a keen interest in the international aspects of medicine, and many of its alumni have made contributions in the international arena. The faculty and students continue to have an active, on-going concern for the health needs of the developing countries of the world.

The faculty of Loma Linda University School of Medicine has high aspirations for its students beyond the wish to see them become scientifically stimulated and competent. The faculty is eager to help its students become physicians in the sense of fulfilling the need that each patient has to identify with a practitioner of medicine. This sensitivity to human need is a quality which should pervade all persons involved in the healing arts and sciences without respect to the discipline practiced—most difficult to teach but so extremely important.

David B. Hinshaw, M.D., Dean

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EDITORIAL

A Problem for the Intellect

There is considerable evidence in both medicine and society that things are moving at a much faster pace than our political and institutional mechanisms were ever designed to handle. Situational changes in the human environment are rapidly outstripping the capability of our research, educational, social, economic or political institutions to find answers to questions which must be answered or solutions to problems which must be solved. Our present institutions often behave like dinosaurs, moving a little faster when the heat is on but slowing down promptly when things cool off and exhibiting an unhappy tendency to get bogged down.

As the pace increases so do the frustrations of those who see the processes of orderly change in our established institutions not only failing to meet the need but falling further and further behind. They therefore come to view the system, or the establishment and its institutions as oppressive, unduly rigid and restrictive, and finally as incapable of ever responding effectively to the problems of the day. Having reached this frustrating conclusion, they seek the means to force a change.

The primitive instinctual approach is to destroy the oppressive thing which stands in the way and many a dinosaur was no doubt destroyed by the activist human beings of earlier days. In more modern times dialogue and discussion, the forte of the intellectual liberals, was tried but failed of sufficient force. It is now undergoing rejection by the body of society. Non-violence and its corollary, the strike, have accomplished much more, and still have the quality of being relatively non-destructive. But these are techniques of the intellect and are primarily of withdrawal. They are too passive to satisfy those whose feelings of frustration and repression are great. These become the activists and sometimes frank revolutionaries. Thus we see what is now called the encounter or confrontation developing in various forms which sometimes lead to change, subsequently the confrontation for confrontation's sake with its inevitable disruption of any sort of progress, and finally the determination to destroy what exists. This is really a return to the primitive instinctual approach although it is more often couched in terms of revolution and a fresh start.

The tragedy is that the frustration which seeks thus to force change is doomed itself to frustration. Human institutions, whether of government, education or of medicine, are necessary and will continue to exist in a complex technologic society. They will not go away. They will arise from the ashes of disruption and destruction and be as frustrating as ever until some intrinsic organizational means are developed for their more rapid adaptation to environmental change, including a capability to anticipate and prepare for the future as well as to store and utilize knowledge and experience acquired in the past. The difficulties of doing this in democratic institutions which must be responsive and responsible to their constituents (and this includes government, educational institutions and organized medicine) are very considerable. This cannot be accomplished by force. It is a problem for the intellect.

The California Medical Association has made a small beginning with its "troika" of planning committees and its recent emphasis on planning and goals. Once the problem is clearly in mind, perhaps physicians can devise an organizational "organism" which will be parabiological in the sense that it will have many of the characteristics of the human organisms of which it is composed, organisms which are at once so general in purpose and yet so easily adaptable to environmental change, often accomplishing this adaptation by modifying the environment itself.

Cancer and the Nervous System

METASTASIS OF CANCER to the central nervous system is well known, but in the past 20 years there has been growing recognition of a group of central and peripheral nervous disorders in cancer, not caused by direct tumor involvement. It has been exciting to neurologists to witness the emergence of a large new class of neurological diseases, but the importance of these diseases lies in their usefulness in diagnosing cancer, as well as the insight they may offer into the pathogenesis of "degenerative" diseases of the nervous system. Some of the remote effects of tumors on other organs are now known to be caused by abnormal production of substances similar or identical to natural hormones. The neurological syndromes, however, are largely unexplained.

The remote effects of cancer on the nervous system can be grouped into two broad categories. On the one hand there are metabolic effects of systemic disturbances like hypercalcemia or hyponatremia; infection by organisms, such as yeast or fungi, to which cancer patients are particularly but not uniquely susceptible; and vascular accidents, such as occur in leukemia and altered clotting states. On the other hand is a group of degenerative or inflammatory diseases of more or less unknown etiologic lineage, some of them seen almost exclusively in association with malignant tumors. Elsewhere in this issue, Rubinstein has thoroughly reviewed the clinical features of the latter group, and his report makes apparent the heavy contributions of English neurologists to this subject, especially the late Lord Brain, P. B. Croft, and Marcia Wilkinson. Despite their efforts, however, classification of these disorders (which they have called "carcinomatous neuromyopathy") still presents difficulties. Not all would agree, for instance, that classical amyotrophic lateral sclerosis occurs with increased frequency in cancer, as claimed by Brain, Croft, and Wilkinson and by Norris and Engel. Certain other spinal cord syndromes in cancer are also not firmly established.

The syndromes which are now widely accepted include: (1) progressive multifocal leukoencephalopathy, a cerebral and rarely spinal demyelinating disease with unique pathological features, occurring mainly in leukemia and lymphoma but also in other cancers and chronic diseases; (2) diffuse polioencephalopathy, characterized by neuronal degeneration in many parts of the neuraxis, and presenting with symptoms of dementia, cerebellar deficit, bulbar palsy, lower motor neuron disease, sensory neuropathy or a mixture of several of these; (3) mixed sensorimotor neuropathy due primarily to segmental demyelination of peripheral nerves; (4) the myasthenic syndrome of Eaton and Lambert, a defect of neuromuscular transmission characterized by paradoxical increase of strength during voluntary effort; and (5) myopathy, including polymyositis and dermatomyositis. It is not uncommon for some of these types to co-exist, adding to the difficulties of classification and diagnosis. This is especially true of the neuromuscular syndromes (which account for more than two-thirds of the cases) in which neuropathy and myopathy may both be present. For this reason some authors, perhaps prematurely, have abandoned distinctions between neurogenic and myogenic weakness in cancer.

How frequent is non-metastatic as compared with the frequency of metastatic disease in cancer? It is surprisingly difficult to discover the incidence of either complication. Metastasis to the brain was formerly said to be observed in 5 percent of cancer patients at autopsy, but more recently figures of 35 percent[1] and 17 percent[2] have been reported (the higher figure includes metastasis within the spinal canal). The only information about the incidence of non-metastatic neurological syndromes comes from Croft and Wilkinson's[3] survey of 1,476 living patients with carcinoma. Seven percent of these patients had clinical evidence of "carcinomatous neuromyopathy," the large majority belonging to the "neuromuscular" type —

proximal weakness, muscle atrophy and loss of reflexes. It is not clear, in the absence of pathological verification, how many of these findings were actually due to carcinomatous neuromyopathy. (Of control patients, 11 percent had some neurological findings.) However, the incidence varied widely with the type of cancer (ranging from 0.5 percent for rectum to 16 percent for ovary or lung), a fact which lends some validity to the diagnoses. Furthermore, in carcinoma of lung and breast the incidence of clinically evident metastatic and non-metastatic complications was about the same — 16 percent. Clearly, however, an autopsy series will be necessary to establish the true incidence of these disorders. On clinical grounds alone, it is quite possible to mistake metastatic for non-metastatic brain disease, and neuropathy may be simulated by meningeal invasion of nerve roots by tumor.

In the case of leukemia and lymphoma, neurological complications are common but are rarely due to progressive multifocal leukoencephalopathy or other neuromyopathy. Spinal cord compression by extradural tumor is the commonest complication of lymphoma. Intracerebral hemorrhage is an important complication of leukemia, and leukemic meningitis is being seen more and more, especially in blastic leukemia, a change attributable to prolonged survival of patients treated with antileukemic drugs which do not enter the nervous system. Infection by yeast, fungi, cytomegalovirus, and other organisms is a constant danger, especially when immunosuppressive agents are used.

The non-metastatic syndromes have one feature of major importance. Except for progressive multifocal leukoencephalopathy they often appear months or years before the underlying malignancy is apparent, and this can alert the clinician to search diligently for the responsible neoplasm. This sequence of diagnosis is already well established in neurological practice and in some cases has led to cure of the malignant lesion. The neuromyopathy itself may improve with treatment of the underlying cancer, but this effect has not been consistent.

The causes of these remarkable diseases may well be diverse. In progressive multifocal leukoencephalopathy the constant finding of intranuclear inclusions in oligodendroglia (the central nervous system cells responsible for formation and maintenance of myelin) early suggested a viral cause. This view has now been strongly supported by electron micrographs from several laboratories showing intranuclear crystalline arrays in oligodendroglia that closely resemble polyoma virus of the papova group.[4] At the other end of the nervous system, Chou[5,6] has reported electron microscopic evidence of particles resembling myxovirus and picornavirus in the muscles of patients with polymyositis and dermatomyositis, though none of the patients had cancer. This preliminary finding is particularly interesting because these myopathic conditions have commonly been attributed to autoimmune processes. Hypersensitivity has also been invoked to explain the rare ganglioradicular sensory neuropathy in cancer, since serum from four such patients was found to contain antibodies reacting with nerve cells.[7] Lymphocytic infiltration and perivascular cuffing have been variably noted in the diffuse polioencephalopathy syndromes, including sensory neuropathy, and a viral cause must still be considered for this group. In recent years, scrapie in animals and kuru and Creutzfeldt-Jakob disease in man, disorders once classified as degenerative and even hereditary, have been transmitted to animals by inoculation of pathological material.[8] Gajdusek and his coworkers[8] at the National Institutes of Health are now investigating other "degenerative" diseases of the nervous system by similar techniques. The studies are slow and expensive, and common diseases like amyotrophic lateral sclerosis and the presenile dementias take precedence, but perhaps these techniques can eventually be used to elucidate the non-metastatic neurological syndromes in cancer.

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Diagnosis of Hyperlipoproteinemias

In the last few years, knowledge of the hyperlipidemias (more precisely, hyperlipoproteinemias) has progressed to the point that we can define certain disorders precisely and manage some of them with impressive results. Others can be categorized but it is not clear that they represent discrete inborn errors of metabolism in the genetic sense.

Division of hyperlipoproteinemias into five types has greatly facilitated diagnosis and management. As Levy points out in his succinct review in this issue of California Medicine, electrophoresis of lipoproteins on paper or other supporting media is being widely adopted as a routine method for this "phenotyping." The procedure is rapid and simple to perform and provides a graphic record. Unfortunately, the patterns often are not clear-cut and experience has shown that they are frequently misinterpreted. When five observers were asked to type 20 patterns from I to V, in only a third was there complete agreement and in only about two-thirds did a given observer make the correct diagnosis as determined by more extensive studies.[1] Last year, a detailed family study was reported[2] purporting to demonstrate dominant inheritance of hyperlipoproteinemia in a family in which some members had type III and others type IV (type III is usually thought to be a recessive trait). The published electrophoretic patterns and other information in this paper have led me to conclude that the author was dealing exclusively with familial type IV disease, a judgment corroborated by others. Such confusion may be somewhat less with agarose or cellulose acetate electrophoresis than with paper, since the pre-beta and beta bands are more clearly separated. However, we have found that particles in the lower size range for chylomicrons are more likely to migrate in the electric field on agarose, a feature of this medium that can lead to classification of type V subjects as type IV.

Our experience with these and other procedures has led us to propose an alternate approach to classification which we believe will be less confusing to the practicing physician.[3] It is based on measurement of cholesterol and triglycerides in fasting serum together with visual assessment of the appearance of the serum after it has been allowed to stand in the cold for one to two days. This method provides both phenotyping and quantitative data essential in evaluation of therapeutic measures. Measurement of cholesterol is readily available to all physicians. Triglyceride measurements are performed in relatively few laboratories.

Recently, a new and extremely simple method for estimating triglycerides has become available.[4] It is based on quantitative assessment of the light-scattering property of the triglyceride-rich, pre-beta lipoproteins in a nephelometer.* Built into the method is detection of chylomicrons (present in type I and type V hyperlipoproteinemias) from measurement of light scattering before and after passing diluted serum through an appropriate microporous filter. With this method, as with electrophoresis, type III remains the chief source of confusion. Type III disease is one of the rarest of the hyperlipoproteinemias (probably second only to type I) and in the great majority of patients can be diagnosed or at least strongly suspected by the presence of planar and tuberous xanthomas. Unequivocal diagnosis of type III hyperlipoproteinemia requires ultracentrifugation of the serum at its own density, followed by demonstration that the lipoproteins floating to the top of the ultracentrifuge tube have beta mobility or abnormal chemical composition. This procedure is currently performed only in a few research laboratories.

Dr. Levy clearly points out that effective treatment is available for two of the three hyperlipoproteinemias that constitute specific disease entities. These are the rare type I and type III disorders, otherwise termed familial hyperchylomicronemia and xanthoma tuberosum, respectively. Treatment of type II disease (familial hyper-beta-lipoproteinemia), a much more common disorder, is acknowledged to be difficult, but the group at the National Heart Institute and others have reported good results with large amounts of the bile acid sequestering agent, cholestyramine. This drug, used to relieve itching in obstructive jaundice, has not been released for other purposes. It seems likely that it or similar agents will become available in the near future.

Our own experience leads us to conclude that patients with endogenous hypertriglyceridemias (types III, IV and V) generally respond well to caloric restriction, which is usually indicated for accompanying obesity. Restriction of simple sugars may also be useful. In addition, limitation of caffeine and nicotine may be helpful, since these drugs increase mobilization of fat from adipose tissue to liver and thus increase formation of endogenous plasma triglycerides. We have also found that excessive intake of ethanol often contributes to severity of hyperlipemia, particularly in type V disease; frequently these patients revert to type IV (disappearance of chylomicrons) when they abstain from ethanol.

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*An instrument designed for this purpose is manufactured by Particle Data, Inc., Elmhurst, Ill.

Type IV disease is by far the most common type of endogenous hypertriglyceridemia. It probably represents a complicated interplay of genetic and environmental factors analogous to the maturity-onset form of diabetes mellitus. The analogy with diabetes extends to the most important environmental "inducer" (overnutrition) and the most important therapeutic measure (caloric restriction). Use of drugs should be limited to those patients who respond inadequately or who are unwilling to adhere to a therapeutic diet. Again, as in diabetes, therapy must be life-long. Experience with one drug, p-chlorophenoxyisobutyrate (Atromid-S), has been rather extensive, but certain untoward effects have recently been reported and the mechanism by which it lowers triglycerides is unknown. According to Strisower, in type IV disease this drug often fails to reduce cholesterol levels as triglyceride levels fall.[5] This has also been our experience in patients who have responded partially to diet and it indicates that levels of cholesterol-rich beta lipoproteins are increasing as the levels of triglyceride-rich pre-beta lipoproteins are reduced. Whether such a result is desirable or undesirable is unknown.

Accumulated evidence from several types of investigation provides a rational and reasonably persuasive argument for treatment of hyperlipoproteinemias as a method to delay or prevent complications of atherosclerosis. It has been pointed out earlier in these columns that we reduce levels of blood glucose in insulin-independent diabetics for reasons that are, if anything, less clear.[6] Our diagnostic tools for the hyperlipoproteinemias have improved remarkably and it is irrational to ignore these methods which provide the basis of treatment specific for definable disorders of lipid transport.

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Health Teams

HEALTH TEAMS are not new in medicine, but they are increasingly important. The need for health teams results primarily from the accomplishments of scientific technology. No single physician nor anyone else can perform every service that even a single patient may require, let alone single handed render all the health care a community, the environment, or the species itself needs or should have. Health professionals can substantially extend the reach of scarce, highly trained personnel, such as physicians and dentists for example, and make them far more productive. Furthermore, only combinations of health professionals can deal effectively with many of the technologically complex problems. Health teams are the order of today and surely they will be of tomorrow. They will not only increase the amount and quality of health care rendered but they will also increase the cost.

If health teams are likely to play so important a role in health care delivery, they should be carefully examined and studied. It is necessary to begin with some sort of definition. The Second Planning and Goals Conference, sponsored by the Committee on Continuing Education of the California Medical Association, proposed a definition which says, "The health team may be defined as a number of persons in the allied health professions and other health personnel associated together to accomplish a common objective in health care by cooperation and coordinated action." This definition has been approved by the Scientific Board and accepted by the Council of the California Medical Association as a basis for further study.

An example of a health team in practice is reported by Martin in this issue of CALIFORNIA MEDICINE. A non-physician team, under physician supervision and direction, performed pelvic examinations and cytologic screening tests in a population group which almost certainly would not otherwise have received this particular health service. Six of 1,400 women screened were found to have cancer which would otherwise not have been detected.

This is an example of but one kind of more or less formalized health team. Others have been reported from time to time in this journal and elsewhere. Like many, it certainly extended the reach of the responsible physician and substantially increased both the quality and quantity of health services to this population group. And although it produced tangible benefit, especially to the six women who were found to have unsuspected cancer, it also added a measurable increment to the over-all cost of medical care.

Health teams can and will improve both the quality and quantity of medical care. It is important that their nature, intrinsic characteristics, and uses be understood by physicians and others. There are many problems pertaining to structure, function, group dynamics, communications, goals, leadership, authority, responsibility, economic efficiency, legal implications and the like which need study and evaluation by all concerned. Health teams are destined to be increasingly important instruments in the delivery of health care services. We look to the California Medical Association for leadership in doing the studies which must be done and in pioneering the broad policy decisions which must be made to make these instruments as effective and efficient as possible for the betterment of the health of us all.

Ghetto Health Care and Medical Schools

THE URBAN GHETTO poses many difficult problems not the least of which is the unanswered question of how best to make modern medical services both accessible and acceptable to ghetto populations. So far it has not been possible to attract a sufficient number of private physicians into these areas to meet the demand. One might speculate whether this would have been any different had financial incentives to practice in these areas been emphasized, rather than criticism of those who earned substantial income from Medicare and Medi-Cal because of services performed in the ghettos. However this may be, other approaches are being sought. Neighborhood health centers of one sort or another under various auspices are being tried and appear only to meet with partial acceptance and success.

More recently a number of medical schools have sought or been encouraged to undertake direct delivery of comprehensive health services to ghetto populations, the presumption being that this will serve the best interests of both. There is good reason to believe, however, that this may not always be the case, if indeed it can ever be so. If they are to render comprehensive health care in the modern sense, the medical school and its faculty must accept a greatly expanded service responsibility, and this can only be at the expense of their primary teaching and research effort. And the ghetto populations must accept the role of teaching patient as being something other than dehumanizing, debasing and discriminatory if the arrangement is to be acceptable to them. For these two reasons the alliance at best would appear to be an unnatural one, and most likely doomed.

Yet the pressure is on, and the pressure appears to be partly financial and partly political. Perhaps significantly it was the private schools in the large communities which first showed the most interest. These are the schools which are apt to have the greater financial need and the greater dependence upon community support, but which are the less subject to political pressure. More recently the public medical schools which are the more dependent upon public and political support are being urged as a matter of social responsibility to take on at least some of the problems of ghetto health care which have so far defied both professional and political solution.

Problems in ghetto health care certainly exist in California and there is increasing evidence of public and political pressure upon the medical schools of the state to become more directly involved in the effort to find solutions. To the extent that this involvement enhances and does not impair their primary and non-transferable responsibilities for production of new physicians and other health personnel, and for research (including research in health care delivery), it should be encouraged and supported. But it is unreasonable and short-sighted to direct the energy and resources of these great educational institutions from what they can do, what only they can do, and what so sorely needs to be done, to a task which they manifestly can never do well, if at all. The delivery of health care in the ghettos is a problem for the professions, the communities and the people in the ghettos themselves to solve. Medical education can make important contributions but it cannot take the professions, the community or the politicians off the hook by assuming such a service responsibility, nor should it be expected to.

LETTERS *to the Editor*

On Polluting the Biosphere

To the Editor: I agree completely with your editorial on "Polluting the Biosphere." (Calif. Med., 110:350-351, April 1969.)

It's a national disgrace that one of our Great Lakes is stinking and dead from man's careless pollution. We are messing our nest, intolerably.

The medical profession is in a unique position to educate and pressure local communities to take effective pollution control action. This is clearly a health matter, and I have found that the "MD" carries weight in discussing environmental quality.

The technology for pollution control is available. What is lacking is public awareness and determination to clean our nest. Here, the medical profession has been as lazy as everyone.

There are new federal and state anti-pollution laws, but much control remains at the hometown level. If the local community does not act, the state and federal controls come into effect.

Doctors talk a lot about the encroachment of "Big Government" into medical matters. Here's a chance for them to DO something — to take action on a local matter before the state and federal authorities move in.

Do you think "pollution nuts" are just a bunch of alarmists? If so, try on for size the writings of Dr. LaMont C. Cole, Cornell biologist. Remember how great big important Man depends completely on a lot of tiny plants for life? Remember photosynthesis and nitrogen cycles? Ponder these thoughts of Dr. Cole, next time you doctors wonder why you should care about all this stuff:

A type of ocean algae, marine diatoms [Dr. Cole says] "produce some 70 percent of the earth's annual supply of oxygen. . . . If we should inadvertently kill enough marine diatoms or the organisms they depend on for fixed nitrogen, we should start running out of oxygen to breathe. Yet these organisms are now being exposed to our half million chemicals. There is evidence that the insecticide DDT can suppress photosynthesis in bodies of water. . . .

"More frightening yet to me [Cole] are the herbicides or 'weed killers'—chemicals specifically designed to be poisonous to plants. At present the military is taking most of our production of these chemicals and shipping it to Vietnam to kill rice and defoliate jungle vegetation. What will happen if a few tankers loaded with concentrated herbicides are sunk in the Pacific? . . ."*

We won't need a nuclear holocaust to finish us off.

FREDERIC A. LANE, M.D.
Bakersfield

Induced Abortion and the Law

To the Editor: "Wider public knowledge" of the lethal danger of gas embolus in induced abortion is urged by Dr. Lester T. Hibbard in your April issue.

As one with some experience in disseminating public knowledge and examining its effects, may I suggest that all the knowledge in the world will not keep desperate women from visiting criminal abortionists or attempting self-induced abortions.

Only a new orientation in the law's philosophy will prevent these needless deaths, and that philosophy must recognize the right of any woman to bear a child or not to bear one. Anything less, including Cailfornia's so-called "liberalized" abortion law, denies this fundamental right to women and limits the right of physicians to practice their profession with unfettered concern for the total health of their patients.

DAVID PERLMAN
Science Editor
San Francisco Chronicle

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*Dr. Cole's quotation taken from "Man and the Air," Population Bulletin Number 5, December 1968, published by the Population Reference Bureau, Inc., 1755 Massachusetts Ave. N.W., Washington, D.C. 20036.

Your Office Assistant and the CMAA

To the Editor: In this age of third party medicine, it has become increasingly important to have an office assistant who is well informed and up to date on office procedures and insurance matters. The girl you now have in your office may already be highly efficient in *your* eyes, but if she exchanges views and ideas with other medical assistants in the local chapter of the California Medical Assistants' Association, you will probably find both you and your assistant will profit immensely. Almost every county in California now has such a chapter and many girls attend the regular meetings locally.

The California Medical Assistants' Association can in no way be construed as a union. The bylaws of the organization specifically preclude the use of the organization as a bargaining agent. Its sole purpose is to upgrade the standards of medical assistants. It seems only logical, therefore, that a physician should pay the dues and other incidental expenses of at least one girl in his office to belong to the medical assistants' organization. The benefits your girl will derive from these meetings will more than pay for her dues and incidentals, such as dinner meetings. Many physicians have found that it pays to have all their girls belong and to pay their expenses.

It is sometimes thought this organization is primarily a social one. While this is not the case, I would like you to keep in mind that most medical societies, in this state and throughout the United States, have dinner meetings to get their members together. It is not illogical, then, to assume if it is made a little more appealing to the girls they will attend the meetings and, by their attendance, cannot help absorbing some of the information brought to them through their meetings. Most local organizations in the state have monthly programs of interest both to registered nurses and the office staff. The topic may be on some aspect of medicine, or the speaker may represent an insurance company, California Blue Shield, or a malpractice carrier. In many locales the girls get to know personally the representative from CBS or Blue Cross, as well as other agencies. This is of value when processing claims, which is, of course, of prime importance in our offices at this time and will undoubtedly become increasingly important.

If you are spending $100 a year on accounting and financial aid, which is deductible, you will find that an equal amount spent on having your office assistants participate in meetings of the California Medical Assistants' Association, will be deductible and help increase their—and therefore your—efficiency. Your girls are desirous of improving themselves to better serve you. This is an excellent way to achieve both. It may also lead to further harmony in the office, since it can easily be considered a fringe benefit by the girls (and helps score points with the help).

This letter is being written primarily because medicine's image has become somewhat tarnished. Part of the difficulty lies in the handling of insurance claim forms and the relationship of the patient with the doctor's staff. It is felt by the California Medical Association, California Blue Shield, and the chapters of the Foundation for Medical Care in the state, that this organization of medical assistants, if successful in its aspirations, can not only improve the physician's image, but can actually help to increase his efficiency through the proper handling of claim forms in the offices.

The present goal of the recently installed president of CMAA, Mrs. Carola Abrams, is to increase enrollment in the organization to such an extent that every office in the state would be represented by at least one girl. If she achieves this goal, we feel that approximately two years under the present program set up by the organization will result in substantial advances in both medicine and medical economics within the state.

WILLIAM M. HEBERT, M.D.
Stockton

Letter to a Medical Student

NOTE: *The following letter was sent by its author to a medical student who was receiving* CALIFORNIA MEDICINE *as a gift from him under the "Bridge the Generation Gap" subscription plan.*

I understand that you will be receiving my gift subscription to CALIFORNIA MEDICINE, not bad as a medical journal and containing news of affairs in California Medical Association. This program of gift subscriptions has been undertaken as an effort to improve communication and understanding between the members of your generation of doctors and mine. Many of us are quite troubled about the things that are said and done by students these days, even medical students, and we hope that future doctors will act and choose on the basis of a valid understanding of the present and the past rather than err because of unnecessary misunderstandings.

Let me tell you something about myself. I am 41 years old, graduated from U.S.C. in 1953 and completed my Boards in Psychiatry in 1960. I have been in private practice since 1957 but have done considerable institutional work in hospitals, clinics, and prisons until 1965 in order to broaden my experience and maintain some steady income to balance the unpredictability of private practice. I joined the AMA in 1962 because it was required where I worked, not because I was particularly attracted to organized medicine. In 1964 I accepted chairmanship of our local LACMA District Forensic Medicine Committee, and began attending Board meetings of our District in that capacity. Since then I have become a dedicated member of LACMA and the CMA, and even of such "right-wing" organizations as AAPS and the Congress of County Medical Societies. I now donate considerably to political campaigns, something I did little before 1964, and I spend many hours working to resist unsound socialistic trends in American life.

I tell you all this so that you will realize I was not always so "square." As you may know, psychiatrists are mostly oriented toward the "left-wing," and I was certainly among them. Obviously, in the last five years, I have begun to see life and values in a different way. Experience in psychiatry has forced me to understand quite differently what makes people "mentally ill" and what helps them to get better. Once I understood the need for a change in psychiatry, I clearly saw the need for a change in all of my political beliefs because the supposedly "scientific" basis of psychiatry is really the philosophy of John Dewey, Sigmund Freud, and earlier Jacques Rousseau; these fellows and their ideas have been around long enough to demonstrate convincingly that their thinking has left out rather large chunks of truth that must somehow be rediscovered if we hope to return ourselves and the world to some kind of sanity before things get much worse. Two years ago, I married a Dane who became an American citizen because of her distress about what socialism has done to her homeland; as you probably know, the Danes are well ahead of us in socialism so their experience can instruct us about what to expect. Many of those who advocate socialism do not advertise the fact that socialism has not brought the good to these countries as expected.

I do not know whether you will find use for CALIFORNIA MEDICINE; if you do not, perhaps you will transfer the subscription to someone who will. I do not know what your political orientation may be, or whether you would want to communicate with me. However, I am willing to respond to any questions or comments you and your friends might wish to make. I am committed to do whatever I can to preserve and improve the good in America and to resist the bad; in this way, regardless of the outcome, I can feel I did my part as a physician and a citizen in this great country of ours.

I hope this letter finds you doing well. The days of medical training were never easy for me, but then, life itself has not been easy and probably never will be. Please feel free to respond in any way you like.

RICHARD R. PARLOUR, M.D.
Claremont

Diagnosis and Treatment of Lipid Transport Disorders

ROBERT I. LEVY, M.D.

Material Supplied by the California Heart Association

ALL THE BLOOD LIPIDS circulate bound to specific proteins. When lipid transport is viewed in terms of these lipid transport proteins (lipoproteins) rather than in terms of any individual lipid (cholesterol, triglyceride), greater specificity and definition can be imparted to the study and understanding of lipid transport disorders.

The differentiation of hyperlipoproteinemia may be accomplished by sequential preparative or analytical ultracentrifugation. For most clinical purposes simpler electrophoretic systems are adequate. Using paper or agarose gel electrophoresis one can obtain patterns that correlate well with ultracentrifugal patterns and at a fraction of the cost. Lipoprotein electrophoresis on paper and gel is rapidly becoming a routine procedure offered by many commercial and hospital laboratories.

There are at least five abnormal lipoprotein patterns that may be associated with hyperlipidemia. Each pattern is distinguished by an increase or abnormality in one or more of the normal serum lipoproteins. The lipoprotein patterns are not necessarily specific for a single disease. They may be primary, many of which are also familial, or secondary to a host of different acquired disorders. The abnormal patterns are accompanied by clusters of clinical manifestations that allow them to be considered different syndromes.

Type I. This lipoprotein pattern is indicative of an inability to clear dietary fat (chylomicrons). It is nearly always familial and in its severe form a rare disorder. The patients are usually young and have creamy plasma, lipemia retinalis, hepatosplenomegaly, eruptive xanthomata and bouts of abdominal pain associated with ingestion of dietary fats. After standing in the cold a discrete cream layer forms in the plasma of these patients. Plasma cholesterols may be normal or elevated; triglyceride concentrations are grossly elevated (often above 5,000 mg%). The familial disorder is recessively transmitted and is characterized by a deficiency in one or more of the enzymes involved in the clearance of fat from the circulation. Therapy is relatively simple. Diets low in fat result in a dramatic clearing of the hypertriglyceridemia and resolution of the associated abdominal complaints. There is no effective drug available now for the treatment of Type I. Supplementation of the diet with medium chain length triglycerides (MCT) often makes the diet more palatable.

Type II or hyperbetalipoproteinemia is a common pattern found at all ages. It is characterized by a marked increase in otherwise normal beta lipoproteins. Though the plasma is almost always clear, cholesterol levels are often in the 300-600 mg% range with normal or only modestly elevated plasma triglycerides. Type II patients may have xanthelasma, arcus juvenalis and tendon and tuberous xanthomata. Of note is the associated premature coronary vessel disease and the often striking family history of early death. This makes it important for all physicians to recognize that the Type II abnormality is often familial and transmitted as a dominant trait with essentially complete penetrance. Though the Type II pattern may be secondary to excessive dietary cholesterol intake, myxedema, myeloma, liver disease or nephrosis, these causes can be quickly evaluated; and when ruled out, a Type II patient's family should be screened for the patient's mother or father and 50 percent of the patient's siblings and children (diagnosable as early as age one) will have hyperbetalipoproteinemia. Therapy for all of the secondary hyperlipoproteinemias should be directed at the acquired problem, i.e., thyroid replacement for myxedema. When this is not possible or the disorder is primary, specific therapy should be directed to the hyperlipoproteinemia. Dietary therapy for Type II emphasizes a reduction in cholesterol content to below 200 mg per day (avoidance of eggs, many dairy products, and fatty meats) and consumption of increased amounts of

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Dr. Levy is Head, Section on Lipoprotein, Laboratory for Molecular Diseases, National Heart Institute, National Institutes of Health, Bethesda, Maryland.

polyunsaturated fats. Most of the drugs available for hyperlipoproteinemia have little effect. Cholestyramine, a bile acid sequestrant, in doses of 16-32 grams per day, has resulted in impressive reductions in cholesterol and betalipoprotein levels. With a combination of a low cholesterol diet and cholestyramine lipid levels can often be brought into the normal range in the Type II subject.

Type III is a relatively uncommon pattern associated with the presence in plasma of abnormal beta lipoprotein forms. Patients have clear, cloudy, or milky plasma with elevations of both cholesterol and triglyceride concentrations into the 350-800 mg% range. These patients often present in the third or fourth decade with planar xanthomata (orange-yellow lipid deposits in the creases of the palms of the hands) as well as tuberoeruptive (elbows, knees, and buttocks) and tendon xanthomata. Commonly, both premature coronary and peripheral vessel disease occur. Type III is usually familial and apparently transmitted as a recessive trait. Dietary therapy for Type III emphasizes calorie control and a diet balanced in fat, carbohydrate, and protein and low in cholesterol. Clofibrate, 2 grams per day, is delightfully effective, especially when coupled, with the balanced therapeutic diet: it results in a complete normalization of plasma cholesterol and triglyceride concentrations, resolution of external xanthomatosis and apparent improvement in pheripheral vessel flow.

Type IV is a very common lipoprotein pattern, most frequently seen after the second decade of life and often associated with diabetes mellitus and premature atherosclerosis. It is characterized by an isolated increase in endogenous triglyceride (prebetalipoproteins). The plasma may be clear, cloudy or milky depending upon the triglyceride concentration. Cholesterol levels are frequently normal. The patients usually have no external stigmata. The pattern sometimes reflects a familial disorder transmitted as a dominant with delayed expression. It may be that several different mutations are responsible. It is often, however, secondary to other metabolic disorders and whether primary or secondary it is usually exacerbated by obesity. Dietary therapy emphasizes reduction to ideal body weight, and reduction in the carbohydrate and alcohol content of the diet with a concomitant increase in the amounts of polyunsaturated fats. Diet therapy alone often results in total normalization of the plasma lipids in Type IV. Drugs like clofibrate, D-thyroxin and nicotinic acid have been variably effective.

Type V is frequently seen secondary to acute metabolic disorders like diabetic acidosis, pancreatitis, alcoholism and nephrosis though it may be familial. Patients with Type V usually become symptomatic after age 20 and may have all the features of Type I: creamy plasma, hepatosplenomegaly and bouts of abdominal pain often with frank pancreatitis. The patients often have multiple abdominal scars after years of occult abdominal pain. They appear to be intolerant to both dietary and endogenous fat and have triglycerides in the 1,000-6,000 mg% range with mildly to markedly elevated plasma cholesterols on an unrestricted diet. Abnormal glucose tolerance and hyperuricemia are frequently associated. Diet therapy emphasizes caloric restriction, reduction to ideal body weight and a diet high in protein and low in carbohydrate and fat. Clofibrate, D-thyroxin, nicotinic acid, may all modestly reduce the triglyceride concentration, but often not to a significant degree.

The importance of going beyond the simple determination of cholesterol and triglyceride should be apparent. Five different types of hyperlipoproteinemia have been briefly characterized and discussed. Each is associated with a specific lipoprotein pattern, that may be familial or acquired. Each is associated with specific clinical and laboratory signs and at least three of the Types (II, III, and IV) are associated with premature vascular disease. Each type responds differently to dietary manipulations and specific drug regimens. Perhaps for the first time, it is now possible for the clinician to apply relatively specific therapy to the patient with a lipid transport disorder.

In Memoriam

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

Beck, William Armond, Sr., Los Angeles. Died 14 April 1969 in Los Angeles of pneumonia, aged 75. Graduate of Meharry Medical College, Nashville, Tennessee, 1921. Licensed in California in 1949. Doctor Beck was a member of the Los Angeles County Medical Association.

⁂

Cerda, Bernardino Botello, Merced. Died 30 March 1969 in Merced, aged 46. Graduate of Universidad Nacional Facultad de Medicina, Mexico, D.F., 1948. Licensed in California in 1952. Doctor Cerda was a member of the Merced-Mariposa Medical Society.

⁂

Diskin, Herman Edward, Los Angeles. Died 29 April 1969 in Los Angeles of coronary artery disease, aged 58. Graduate of Wayne University College of Medicine, Detroit, 1940. Licensed in California in 1944. Doctor Diskin was a member of the Los Angeles County Medical Association.

⁂

Hendricks, Coleman Bresee, Los Angeles. Died 25 March 1969 in Los Angeles of cancer, aged 63. Graduate of the University of Southern California School of Medicine, Los Angeles, 1937. Licensed in California in 1937. Doctor Hendricks was a member of the Los Angeles County Medical Association.

⁂

Hutson, Seba Ford, Jr., Long Beach. Died 4 May 1969 in Long Beach of acute blastic leukemia, aged 45. Graduate of University of Southern California School of Medicine, Los Angeles, 1952. Licensed in California in 1952. Doctor Hutson was a member of the Los Angeles County Medical Association.

⁂

MacRae, Herbert Bennett, Castro Valley. Died 27 March 1969 in Castro Valley, aged 69. Graduate of Tufts College Medical School, Boston, 1933. Licensed in California in 1935. Doctor MacRae was a member of the Alameda-Contra Costa Medical Association.

⁂

Markthaler, Edward Leopold, Santa Barbara. Died 15 April 1969 in Santa Barbara, aged 74. Graduate of Columbia University College of Physicians and Surgeons, New York City, 1923. Licensed in California in 1926. Doctor Markthaler was a member of the Santa Barbara County Medical Society.

⁂

Milum, Edward W., Newport Beach. Died 22 March 1969 in Newport Beach, aged 62. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1935. Licensed in California in 1935. M.D. degree from California College of Medcine, 1962. Doctor Milum was a retired member of the Forty First Medical Society and the California Medical Association, and an associate member of the American Medical Association.

⁂

Newman, Meyer Harris, Beverly Hills. Died 12 April 1969 in Santa Monica of congestive heart failure, aged 88. Graduate of University of Nebraska College of Medicine, Lincoln, 1910. Licensed in California in 1925. Doctor Newman was a member of the Los Angeles County Medical Society.

⁂

Northway, Frederick James, San Francisco. Died 23 April 1969 in San Francisco of heart disease, aged 61. Graduate of Stanford University School of Medicine, Palo Alto, 1937. Licensed in California in 1937. Doctor Northway was a member of the San Francisco Medical Society.

⁂

Robinson, Stanley T., San Jose. Died 15 November 1968 in San Jose of heart disease, aged 46. Graduate of University of Oregon Medical School, Portland, 1946. Licensed in California in 1953. Doctor Robinson was a member of the Santa Clara County Medical Society.

⁂

Rowan, Edmund James, Wilmington. Died 22 April 1969 in Long Beach of uremia with acute circulatory failure, aged 90. Graduate of Rush Medical College, Chicago, 1903. Licensed in California in 1922. Doctor Rowan was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

⁂

Russell, Ray M., Lancaster. Died 9 April 1969 in Lancaster, aged 76. Graduate of Chicago College of Osteopathy, 1923. Licensed in California in 1940. M.D. degree from California College of Medicine, 1962. Doctor Russell was a member of the Los Angeles County Medical Association.

⁂

Sanden, Austin O., Bakersfield. Died 18 March 1969 in Salado, Arkansas, aged 81. Graduate of University of Oklahoma School of Medicine, Oklahoma City, 1922. Licensed in California in 1926. Doctor Sanden was a retired member of the Kern County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

Schumacher, Martin John, Beverly Hills. Died 25 April 1969 in Huntington Beach of heart disease, aged 49. Graduate of Marquette University School of Medicine, Milwaukee, 1945. Licensed in California in 1945. Doctor Schumacher was a member of the Los Angeles County Medical Association.

✣

Stahlman, Gray E. B., San Jose. Died 11 April 1969 of cancer of the lung, aged 47. Graduate of Vanderbilt University School of Medicine, Nashville, Tenn., 1950. Licensed in California in 1961. Doctor Stahlman was a member of the Santa Clara County Medical Society.

von Seeth, Edward H., Atascadero. Died 14 April 1969, aged 63. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1930. Licensed in California in 1930. M.D. degree from California College of Medicine, 1962. Doctor von Seeth was a member of the San Luis Obispo County Medical Society.

✣

Weil, Solomon Neubauer, Rodeo. Died 6 April 1969 in San Pablo of myocardial infarction, aged 71. Graduate of University of Oregon Medical School, Portland, 1924. Licensed in California in 1924. Doctor Weil was a member of the Alameda-Contra Costa Medical Association.

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PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H. Director, State Department of Public Health

Hyaline Membrane Disease

An estimated 4,000 infants are born each year in California with the respiratory distress syndrome —so-called hyaline membrane disease. This disorder accounts for approximately 25 percent of infant deaths occurring in the first 28 days of life. The incidence is correlated with birth weight and is highest among very small prematures, over 90 percent of the cases being in infants under 2,500 grams. The disease develops in approximately 15 to 20 percent of infants with birth weights under 2,500 grams. The highest mortality rate from the disease is also reportedly in small prematures — 70 percent.

The disease usually runs a rapid course over the first few days of life. Unless there is clinical improvement during this period, followed by gradual clearing of x-ray findings over a period of one to two weeks, the infants die. Potential complications of the disease, or conditions coinciding with it, such as brain hemorrhage, pulmonary hemorrhage, collapse of the lungs or certain congenital anomalies, require highly specialized care. Following the acute stage, the infants need care until they reach a weight which makes it safe to discharge them from the hospital. This means an average of three to four weeks of additional stay in hospital.

In recent years several hospitals have developed intensive care nurseries to provide specialized care for such infants. The initial reports from these hospitals indicate that an improvement in mortality rate is experienced and surviving infants suffer little permanent damage. This approach is extremely costly, and detailed analysis will be required to evaluate it before extending it can be generally recommended.

The California Legislature has taken considerable interest in this disease. In 1967 it passed ACR 108, requesting the State Department of Public Health to study the disease, its treatment and cost, and to report to the Legislature. During the 1968 session, the Legislature passed AB 1413, to take effect in November, 1968, requiring the Department to evaluate further, in a three-year pilot project, the cost and effectiveness of treating the disorder and to make annual progress reports.

The Department's Bureau of Maternal and Child Health began to implement the law by surveying all 413 California hospitals with maternity services to find out the number and distribution of intensive care nurseries. Fifty-nine of the 413 claimed to have such a unit, but telephone inquiries and site visits determined that only 15 such operating units of varying size could be properly classified as ICN units. (Some hospitals appeared to be describing premature units—that is, isolettes or incubators — rather than true intensive care nursery [ICN] units with monitoring devices.)

Sixty-five stated that they are considering the possibility of adding such a unit and 289 hospitals indicated that they had no plans for ICN units. There are ICN units in operation in Alameda, San Francisco, Santa Clara, Los Angeles, San Bernardino and Orange counties, and others are planned in San Diego, Fresno and Sacramento counties. Pregnant women with a history of premature delivery or at risk of it should be admitted to a hospital where specialized care is available. Premature babies born where such units are not available should be transported in ambulances specially equipped to care for them and accompanied by at least one trained person enroute to an ICN.

Plans for carrying out the provisions of AB 1413 call for both retrospective and prospective studies of the disease. The frequency and degree of severity of the disorder, cost and effectiveness of treatment and final outcome in a representative population of newborns during 1965, before the advent of specialized ICN units, will be studied. This will involve a review of over 3,500 premature births and 700 perinatal deaths in 1965, to determine mortality and long-term morbidity. The study will estimate the costs of treatment of this disorder to the individual, the community and the state, in 1965.

At the same time, the Department will conduct a continuing study of cases occurring in 1969, 1970 and 1971 in which the patients are cared for in intensive newborn care units, and will compare results and costs with the experience in the same hospitals before the ICN unit was established. An ad hoc advisory group of the California Medical Association, consisting of specialists in care of the newborn, will assist the Department in designing a competent and definitive study of the disease. The advisory committee reviewed and approved initial Department protocol and the program is now in operation.

Perhaps the most significant by-product of the Department's study of hyaline membrane disease will be an examination and review of current nursery practices in hospitals. At present, there is much variation among hospitals as to how their nurseries are arranged and as to which areas infants are assigned. A definition of intensive care nursery units and a better description of modern nursery practices ought to come out of this study, and that should aid the Department in revising hospital licensing and certification laws in this field.

"COLDS" AND COW'S MILK

"I'm impressed with how frequently perennial allergic rhinitis in children, often misinterpreted as repeated colds or chronic colds, is actually due to reactivity to cow's milk. (I say reactivity because I don't know what this is. In some hands, it's associated with a large measure of precipitin reactivity in the serum against cow's milk or some of its products; in other hands, this is not so easily demonstrated.) But I think a trial diet free of cow's milk for the child who has chronic upper respiratory problems should be given a chance."

—Victor C. Vaughn, III, M.D., Philadelphia
Extracted from *Audio-Digest Pediatrics,* Vol. 14, No. 22, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

EDUCATION NOTICES

Meetings and Courses

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of the dates of continuing education programs and the meetings of various medical organizations in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102; or phone: (415) 776-9400, extension 241.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Postgraduate Course Information

CMA:	**California Medical Association** For information contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. (415) 776-9400, ext. 241.
LLU:	**Loma Linda University** For information contact: John E. Peterson, M.D., Associate Dean for Research Affairs, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.
PMC:	**Pacific Medical Center** For information contact: Arthur Selzer, M.D., Chairman, Education Committee, Pacific Medical Center, Clay and Webster Streets, San Francisco 94115. (415) 931-8000.
STAN:	**Stanford University** For information contact: Thomas A. Gonda, M.D., Associate Dean, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5940.
UCD:	**University of California, Davis** For information contact: Charles J. Tupper, M.D., Dean, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0333.
UCI:	**University of California — California College of Medicine, Irvine** For information contact: Robert Combs, M.D., Associate Dean, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.
UCLA:	**University of California, Los Angeles** For information contact: Donald Brayton, M.D., Associate Dean and Head, Continuing Education in Medicine and the Health Sciences, 15-39 Rehabilitation Center, UCLA Center for the Health Sciences, Los Angeles 90024. (213) 825-6514.
UCSD:	**University of California, San Diego** For information contact: Clifford Grobstein, Ph.D., Dean, University of California, San Diego, School of Medicine, La Jolla 92038. (714) 453-2000.
UCSF:	**University of California, San Francisco** For information contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, Health Sciences, University of California Medical Center, San Francisco 94122. (415) 666-1692.
USC:	**University of Southern California** For information contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 225-1511, ext. 203.

CANCER

September 26-27—**Current Concepts in Medical Oncology.** Medical Oncology Service, Mt. Zion Hospital and Medical Center at Mt. Zion Hospital, San Francisco. Friday-Saturday. Contact: Ernest H. Rosenbaum, M.D., Director, Medical Oncology Service, Mt. Zion Hospital and Medical Center, 1600 Divisadero, San Francisco 94115. (415) 567-6600.

November 1—**Current Concepts in Cancer.** UCSF at Children's Hospital, San Francisco. Saturday.

November 15-16—**Fifth Annual Clinical Cancer Conference.** UCSF. Saturday-Sunday.

December 7 — **California Tumor Tissue Registry — Semi-Annual Cancer Conference.** Beverly Hilton Hotel, Beverly Hills. Sunday. Contact: W. K. Bullock, M.D., Exec. Dir., Los Angeles County Hospital, 1200 N. Lake St., Los Angeles 90033.

MEDICINE

July 24-26 — **Diseases of the Colon and Anorectum.** UCLA at Wadsworth V.A. Hospital, Los Angeles. Thursday-Saturday.

July 31 - Aug. 2 — **Clinical Decisions in Cardiology.** Council on Clinical Cardiology, American Heart Association, California and San Francisco Heart Associations. Hilton Hotel, San Francisco. Thursday-Saturday. Contact: Local Heart Association.

August 16—**Electrocardiography.** PMC. Saturday.

August 17-20—**Advanced Seminars in Internal Medicine.** UCLA at Lake Arrowhead. Sunday-Wednesday.

August 25-29—**American Physiological Society.** Davis. Monday-Friday. Contact: Ray G. Draggs, Ph.D., Exec. Sec.-Treas., 9650 Rockville Pike, Bethesda, Md. 20014.

August 26-Sept. 1—**Pacific Dermatological Association.** Princess Kalulana Hotel, Honolulu. Tuesday-Monday. Contact: John M. Shaw, M.D., Sec.-Treas., 419 South L Street, Tacoma, Wash. 98405.

September 9-10—**19th Annual Professional Symposium on Cardiovascular Diseases.** San Diego County Heart Association in cooperation with USC at Hilton Inn, San Diego. Contact: James E. Lasry, M.D., Symposium Chairman, 3330 - 3rd Avenue, San Diego 92103.

September 13-19 — **American Electroencephalographic Society.** El Cortez Hotel, San Diego. Saturday-Friday. Contact: Philip T. White, M.D., 8700 W. Wisconsin Ave., Milwaukee 53226.

September 14-20 — **International Congress of Electroencephalography & Clinical Neurophysiology.** El Cortez Hotel, San Diego. Sunday-Saturday. Contact: Richard D. Walter, M.D., Congress Sec. UCLA.

September 29 - Oct. 10 — **Intensive Review of Internal Medicine.** USC. Monday-Friday, Two weeks. $150.

October 1-3 — **Annual Postgraduate Symposium on Heart Disease.** St. Francis Hotel, San Francisco. Wednesday-Friday. Contact: Gene C. Taylor, Executive Director, San Francisco Heart Assoc., 259 Geary Street, San Francisco 94102.

October 7 — **Evening Lectures in Medicine.** UCSF at Oakland Hospital. Tuesday evenings through Dec. 2.

October 10-12—**California Society of Internal Medicine—Scientific Program.** Coronado. Friday-Sunday. Contact: Cynthia Bell, Exec. Sec., 350 Post Street, San Francisco 94108.

October 18—**Arrhythmias.** PMC. Saturday.

October 23—**Hypertension.** USC at Hilton Hotel, Los Angeles. Thursday.

October 29-30—**Symposium of Diabetes.** USC at Hilton Hotel, Los Angeles. Wednesday-Thursday.

October 31 — **Endocrinology — 14th Annual Medical Symposium.** Southern California Permanente Medical Group and Kaiser Foundation Hospitals. Friday. Contact: Shirley Gach, Symposium Coordinator, Rm. 6014, 4900 Sunset Blvd., Los Angeles 90027.

November 2-5—**California Academy of General Practice — 21st Annual Scientific Assembly.** Century Plaza Hotel, Los Angeles. Sunday-Wednesday.

November 7-8—**Physical Medicine and Rehabilitation.** UCSF. Friday-Saturday.

November 12—**Office Dermatology.** USC. Wednesday.

November 13-15—**West Coast Allergy Society.** Hilton Inn, San Diego. Thursday-Saturday. Contact: Betty J. Jones, Exec. Sec., P.O. Box 42067, Portland, Ore. 97242.

November 15—**Gastroenterology.** PMC. Saturday.

Grand Rounds—Medicine

Tuesdays

Medical Grand Rounds: 9-10:30 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

Wednesdays

Grand Rounds in Internal Medicine: UCSF. 10:30-12:00 noon.

USC Department of Medicine Grand Rounds. 11:00 a.m., Room 1645, Los Angeles County-USC Medical Center.

UCI Grand Rounds in Medicine. 12:30 p.m., Auditorium, School of Nursing, Orange County Medical Center.

Grand Rounds in Internal Medicine. 1:30-3:00 p.m., Fresno General Hospital.

Thursdays

Medical Grand Rounds, UCLA. 10:30-12:00 noon, Room C3-105, UCLA Medical Center.

Fridays

Medical Grand Rounds — 8:00 a.m., Courtroom, Third Floor, Kern County General Hospital, Bakersfield. CRMP Area IV.

Medical Grand Rounds — 8:30 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles. CRMP Area IV.

Infectious Disease Grand Rounds—USC. 10:00 a.m., Auditorium, Children's Division Building, Los Angeles County-USC Medical Center, Los Angeles.

Medical Grand Rounds—1st and 3rd Fridays, 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

Medical Grand Rounds — 2-3:00 p.m., Classroom, Third Floor, Fresno General Hospital, Fresno. CRMP Area IV.

Rheumatology Grand Rounds — USC, 11:30 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles.

OBSTETRICS AND GYNECOLOGY

August 13-17—**Second Annual Advanced Seminars in Obstetrics and Gynecology.** UCLA at Lake Arrowhead. Wednesday-Sunday.

September 25-27 — **The Office Practice of Ob/Gyn.** UCSF at Hilton Hotel, San Francisco. Thursday-Saturday.

December 5-6—**Obstetrics & Gynecology.** PMC. Friday-Saturday.

PEDIATRICS

July 11-12—**Pediatric Allergy.** PMC. Friday-Saturday.

September 19-20—**Pediatric Annual Meeting—Medical Staff, Children's Hospital, Oakland.** Highland Inn, Carmel. Friday-Saturday. Contact: Miss Inetta Carty, Children's Hospital, 51st and Grove Streets, Oakland 94609.

September 24-25—**26th Annual Brennemann Memorial Lectures.** Los Angeles Pediatric Society at Sportsmen's Lodge, North Hollywood. Wednesday-Thursday. Contact: Kenneth O. Williams, M.D., Sec.-Treas., P.O. Box 2022, Inglewood 90305.

September 27-28—**Pediatric Neurology.** UCLA. Saturday-Sunday.

September 29-Oct. 10—**Mental Retardation Workshop.** UCLA. Monday-Friday, Two weeks.

October 4-5—**Pediatric Neurology.** UCLA. Saturday-Sunday.

October 6-10—**Pediatric Allergy.** UCSF. Monday-Friday.

October 15—**Newborn Infant Care.** USC. Wednesday.

November 8-9—**Pediatric Neuroradiology.** UCLA. Saturday-Sunday.

November 10-12—**The Fetus and the Newborn.** American Academy of Pediatrics at UCSF. Monday-Wednesday. Contact: William H. Tooley, M.D., 327 Crestmont Dr., San Francisco 94131. (415) 566-7637.

Grand Rounds—Pediatrics

Tuesdays

UCLA. 8:30-9:30 a.m., Sixth Floor Conference Room, Harbor General Hospital, Torrance.

USC. 8:30 a.m., Auditorium, Children's Division Building, Los Angeles County-USC Medical Center, Los Angeles.

8:30 a.m., Conference Room, Sixth Floor, Harbor General Hospital, Torrance. CRMP Area IV.

8:30 a.m., Room 4-A, Kern County General Hospital, Bakersfield. CRMP Area IV.

Wednesdays

UCI. 8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and the Auditorium, Children's Hospital of Orange County.

8:30 a.m., Bothin Auditorium, Children's Hospital, San Francisco.

Thursdays

UCSF. 8:30-10:00 a.m., Room 664, Science Building, UCSF.

Cedars of Lebanon Hospital. 8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

Fridays

8:00 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA. CRMP Area IV.

STAN. 8:30 a.m., Stanford University Medical Center, Palo Alto.

PSYCHIATRY

September 27-28—**NIMH Program—Mendocino Series.** UCSF at Mendocino. Saturday-Sunday.

October 4-5 and 11-12—**Intermediate Methods in Family Therapy.** UCSF at San Joaquin. Saturday-Sunday.

October 7—**Psychiatry and Civil Law.** UCLA. Tuesdays through Dec. 9.

October 18-19 — **Adscititious Therapies in Psychiatry.** UCSF at Agnews State Hospital, San Jose. Saturday-Sunday.

October 20-24—**Group Therapy.** UCSF at V.A. Hospital, San Francisco. Monday-Friday.

October 28-Nov. 2—**American Society of Clinical Hypnosis—12th Annual Scientific Meeting and Workshop.** Jack Tar Hotel, San Francisco. Tuesday-Sunday. Contact: F. D. Nowlin, Exec. Sec., 800 Washington Ave., S.E., Minneapolis 55414.

November 1—**Is Marriage a Mystique?** UCSF. Saturday.

November 1-2 — **NIMH Program—Mendocino Series.** UCSF at Mendocino. Saturday-Sunday.

November 1-2 — **Modern Approaches to Psychiatry.** UCSF at Napa. Saturday-Sunday.

November 11-16—**Society for Clinical and Experimental Hypnosis—21st Annual Meeting.** Stanford University, Palo Alto. Tuesday-Sunday. Contact: Mrs. Mario Kenn, Society for Clinical and Experimental Hypnosis, 353 W. 57th St., New York 10019.

December 6-7 — **NIMH Program — Mendocino Series.** UCSF at Mendocino. Saturday-Sunday.

December 13-14—**Psychiatric Perspectives in Medicine.** UCSF at Stockton State Hospital, Stockton. Saturday-Sunday.

SURGERY

July 24-26—**Strabismus Conference.** PMC. Thursday-Saturday.

August 1-3 — **Monitoring the Anesthetized Patient—Current Trends.** UCLA. Friday-Saturday. $65.

August 21-23—**Retinal Detachment Conference.** PMC. Thursday-Saturday. $125.

September 4-6—**Scoliosis Research Society.** Disneyland Hotel, Los Angeles. Thursday-Saturday. Contact: William J. Kane, M.D., Sec.-Treas., Box 484, University Hospitals, Minneapolis 55455.

September 8 — **Spine Mechanics—Orthopedic Symposium.** Southern California Permanente Medical Group and Kaiser Foundation Hospitals. Statler Hilton Hotel, Los Angeles. Monday, 2-5:30 p.m. Contact: Shirley Gach, Symposium Coordinator, Rm. 6014, 4900 Sunset Blvd., Los Angeles 90027.

September 13—**Hand Injuries.** PMC. Saturday.

October 3-4—**Vascular Surgery.** UCSF. Friday-Saturday.

October 4—**Ophthalmology.** PMC. Saturday.

October 6-10—**American College of Surgeons—Annual Meeting.** Fairmont Hotel, San Francisco. Monday-Friday. Contact: John Paul North, M.D., 55 E. Erie Street, Chicago 60611.

October 14-22—**Pan-Pacific Surgical Association.** Hawaiian Hilton, Honolulu. Tuesday-Wednesday. Contact: Mrs. Harriet N. DeVault, Exec. Sec., Rm. 236, Alexander Young Bldg., Honolulu 96813.

October 25-29—**American Society of Anesthesiologists—Annual Session.** Hilton Hotel, San Francisco. Saturday-Wednesday. Contact: John W. Andes, Exec. Sec., 515 Busse Highway, Park Ridge, Ill. 60068.

October 31-Nov. 1—**Surgical Emergencies.** PMC. Friday-Saturday.

December 4-6—**Management of Uveitis—Annual Proctor Program.** UCSF. Thursday-Saturday.

December 12-14—**Fluid & Electrolytes.** USC at Palm Springs. Friday-Sunday.

Grand Rounds—Surgery

Wednesdays

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

1st and 3rd Wednesdays. 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

Fridays

UCI. 1-2:00 p.m., Auditorium, Orange County Medical Center, Orange.

9:30 a.m., Neuroradiology, 10:15 Neurology, 11:15 Neurosurgery. Stanford University Medical Center, Palo Alto.

Saturdays

9:00 a.m., Room 73-105, Health Sciences Center, UCLA. CRMP Area IV.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

OF INTEREST TO ALL PHYSICIANS

July 2-6—**Seminars for General Practitioners.** UCLA at Lake Arrowhead. Wednesday-Sunday.

July 14-18 — **Hospital Information Systems: Techniques and Applications.** USC School of Engineering. Contact: W. D. Campbell, Coordinator, Noncredit Programs, USC.

August 10-14—**National Medical Association.** Hilton Hotel, San Francisco. Contact: John T. Givens, M.D., Exec.-Sec., 2400 Corprew Avenue, Norfolk 23504.

August 16-27—**12th Annual Postgraduate Refresher Course.** USC at Honolulu and Maui, Hawaii. Saturday-Wednesday.

September 18-20—**Postgraduate Assembly.** St. John's Hospital, Santa Monica. Thursday-Saturday. Contact: John C. Eagan, M.D., Director, St. John's Hospital Postgraduate Assembly, 1328 22nd St., Santa Monica 90404.

September 24 — **Clinical Psychiatry for Non-Psychiatrists: A Course in Medical Psychotherapy.** UCSF. Wednesdays through Dec. 17.

September 25-27 — **Initial Emergency Care.** UCSF. Thursday-Saturday.

October 1-29 — **Pharmacy Evening Lecture Series.** UCSF. Wednesdays.

October 2—**A Course in Mental Retardation for Physicians.** UCSF. Thursdays through May 21.

October 11-12 — **Health of the School Child.** UCSF. Saturday-Sunday.

October 11-12—**Kern Postgraduate Conference.** Kern County General Hospital at Civic Auditorium, Bakersfield. Saturday-Sunday. Contact: George A. Paulsen, M.D., Conference Committee Chairman, 2603 G St., Bakersfield 93301.

October 17-18—**Western Industrial Medical Association.** Jack Tar Hotel, San Francisco. Friday-Saturday. Contact: Mr. B. H. Bravinder, 2180 Milvia St., Berkeley 94704.

October 17-18—**Thirteenth Annual Western Industrial Health Conference.** Jack Tar Hotel, San Francisco. Friday-Saturday. Contact: Mr. B. H. Bravinder, 2180 Milvia St., Berkeley 94704.

October 24-25—**Recreation in Rehabilitation.** UCSF. Friday-Saturday.

October 25-26 — **How the Patient Affects the Doctor.** UCSF at Fresno Community Hospital, Fresno. Saturday-Sunday.

November 15—**Mayo Alumni Association—45th Annual Meeting.** Century-Plaza Hotel, Los Angeles. Saturday. Contact: Office of the 45th Annual Meeting, 5410 Wilshire Blvd., Los Angeles 90036. (213) 931-1621.

November 15-16—**Sex and the Professional Man.** Christian Medical Society at Monte Corona Conference Grounds, Lake Arrowhead. Saturday-Sunday. Contact: Albert Holt, M.D., 4080 Hoking Way, Los Angeles 90027.

November 15-16—**Financial, Tax and Investment Planning.** UCLA. Saturday-Sunday.

December 3—**Postgraduate Assembly—St. Luke's Hospital of Pasadena.** At the Huntington-Sheraton Hotel, Pasadena. Wednesday. Contact: W. K. Bullock, M.D., Chairman, 1969 Postgraduate Assembly, 2632 E. Washington Blvd., Pasadena 91107.

CONTINUOUSLY

Basic Home Course in Electrocardiography. One year postgraduate series, ECG interpretation by mail. Physicians may register at any time. $100 (52 issues). Contact: USC.

Audio-Digest Foundation. A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: General Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Anesthesiology, Ophthalmology. Catalog of lectures and panel discussions in all areas of medical practice also available. Contact: Mr. Claron L. Oakley, Editor, 619 S. Westlake Ave., Los Angeles 90057.

WHERE IT'S AT

"Did any of you ever wonder where all this teen-age intercourse is taking place? . . . The findings of a study recently completed at St. Anne's Maternity Hospital in Los Angeles may come as a shock to you. The most likely place for a teen-ager to become pregnant is in the boy's home. Second most likely place is in her home. The third most likely place is in the private home of another person. Way down on the list are the drive-in and the motel. We forbid our daughters to go to the drive-in movies; and then leave them at home and spend a week-end in Las Vegas."

—Robert A. Sack, M.D., Los Angeles
Extracted from *Audio-Digest Pediatrics,* Vol. 14, No. 23, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

98th annual session program

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98th annual session program

1856

AMBASSADOR HOTEL
LOS ANGELES
MARCH 15 to 19, 1969

SCIENTIFIC SESSIONS • TECHNICAL AND SCIENTIFIC EXHIBITS
MOTION PICTURE SYMPOSIA • VIDEO TAPE TV PROGRAMS
MEETINGS OF THE HOUSE OF DELEGATES

california medical association

CALIFORNIA MEDICAL ASSOCIATION ANNUAL MEETING

March 15 to 19, 1969, Los Angeles

Daily Schedule of Scientific Sessions

Unless otherwise stated, all meeting rooms listed in the programs are in the Ambassador Hotel

SATURDAY, MARCH 15 *MORNING MEETINGS*

Section Meetings:
Pathology

Special Conferences:
Radiology Cancer Conference ALL DAY

AFTERNOON MEETINGS

CMA HOUSE OF DELEGATES—Opening Session (4:00 p.m. sharp)

California Society of Pathologists Meeting

Special Conferences:

Cancer Symposium

Los Angeles and Metropolitan Dermatological Societies Clinical Meeting

SUNDAY, MARCH 16 *MORNING MEETINGS*

Section Meetings:

Allergy and noon lunch
Anesthesiology ALL DAY
Dermatology
Internal Medicine — University of California, Los Angeles
Orthopedics
Otolaryngology
Radiology

Special Conferences:

Pathology Cancer Conference ALL DAY

TELEVISION: (1) Diagnosis and Management of Masses of the Head and Neck, (2) Breast Cancer: New Techniques in Diagnosis and Treatment (LIVE)

NOON

TELEVISION: To be announced. (VIDEOTAPE DEMONSTRATION)

AFTERNOON MEETINGS

General Meeting: Symposium on Stroke

Section Meetings:
Ophthalmology

Special Conferences:

L. Henry Garland Memorial Lecture

MOTION PICTURE PROGRAM: Surgery

MONDAY, MARCH 17 *MORNING MEETINGS*

Section Meetings:

General Practice ALL DAY
Industrial Medicine
Internal Medicine—University of Southern California School of Medicine
Obstetrics and Gynecology ALL DAY (including noon lunch)
Pediatrics
Physical Medicine and Rehabilitation ALL DAY
Psychiatry and Neurology ALL DAY
Urology ALL DAY

Special Conferences:

Emergency Medical Services ALL DAY
Family Life Education: The Role of the Physician and Clergyman ALL DAY

TELEVISION: (1) The Undiagnosed Lung Lesion, (2) Detection of Early Cervical Cancer (LIVE)

AFTERNOON MEETINGS

General Meeting: A Physiologic Basis of Metabolic Disease

Section Meetings:

Preventive Medicine and Public Health

Special Conferences:

AMA Council on Foods and Nutrition

MOTION PICTURE PROGRAM: (1) Lupus Erythematosus, (2) Adolescent Suicide

TUESDAY, MARCH 18 *MORNING MEETINGS*

General Meeting: The Damaged Child: What Is His Inheritance?

Section Meetings:

General Surgery ALL DAY

Pediatrics—Lunch—11:30 a.m.

Special Conferences:

California Medical Assistants Association

TELEVISION: Coronary Artery Disease: Medical and Surgical Management (LIVE)

NOON

TELEVISION: To be announced. (VIDEOTAPE DEMONSTRATION)

AFTERNOON MEETINGS

HOUSE OF DELEGATES (3:00 p.m.)

Section Meetings:

General Practice
Internal Medicine—American College of Cardiology
Pediatrics (following 11:30 a.m. lunch)

MOTION PICTURE PROGRAM: Stroke

WEDNESDAY, MARCH 19 *MORNING MEETINGS*

HOUSE OF DELEGATES — 9:00 a.m. (will continue until business is completed)

Special Conferences:

Treatment and Prevention of Self-Inflicted Drug Overdose

MOTION PICTURE PROGRAM: Cancer

TELEVISION: To be announced (VIDEOTAPE DEMONSTRATION)

Scientific Program

CALIFORNIA MEDICAL ASSOCIATION

Ninety-Eighth Annual Session

Ambassador Hotel

LOS ANGELES
March 15 to 19
1969

HOUSE OF DELEGATES
OPENING MEETING
SATURDAY, MARCH 15
4:00 P.M.

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Information

BADGES—It is important that badges be worn at all times. Admission to scientific meetings is by badge only.

COUNCIL—The Council will meet Friday at 4 p.m., March 14, and 9 a.m. to 4 p.m., Saturday, March 15, East Venetian Room.

HOUSE OF DELEGATES—For meeting times, places and agenda, see pages 28 to 33.

EMERGENCY CALL AND MESSAGES — Convention Emergency Call Number (213) 381-2191 from 8 a.m. to 5 p.m., Saturday, March 15, through Wednesday, March 19.

MESSAGE CENTER (213-381-2191)—*Provided through the courtesy of the Pacific Telephone Company* — Registration Desk, Ballroom Foyer, Casino Floor—Registration Desk is open from 8 a.m. to 5 p.m.—The Association will *attempt* to transmit *emergency* messages to the individual physician. Each physician should notify his own office of the exact times and meetings he plans to attend, and the convention number. Routine messages will be kept at the Message Center in the Ballroom Foyer, Casino Floor, at the entrance to the exhibit area and adjacent to the registration desk. Physicians are requested to check with the Message Center at least once a day.

INDEX TO PARTICIPANTS. See pages 25 to 27.

TECHNICAL EXHIBITS—Ballroom and Foyer, Sunset Room and Boulevard Room, Casino Floor. See page 35.

SCIENTIFIC AND ORGANIZATIONAL EXHIBITS — Ballroom, Casino Floor. See pages 20 to 21.

MOTION PICTURE SYMPOSIA will be shown in the West Venetian Room and Foyer. See pages 23 to 24.

TELEVISION PROGRAMS AND VIDEO-TAPE DEMONSTRATIONS will be shown in the West Venetian Room and Foyer. See page 24.

REGISTRATION AND INFORMATION — Registration and information desks are located in the Ballroom Foyer, Casino Floor, at the entrance to the exhibit area. *All members, guests and visitors are requested to register immediately upon arrival.* There is no charge for registration. Registration desks are open Saturday through Wednesday. *Admission to the general and section sessions, and exhibit areas is by badge only.*

Members wishing to vote in specialty sections must indicate appropriate section when registering; voting in other sections will not be allowed.

QUALIFICATIONS/REQUIREMENTS FOR REGISTRATION—(a) All M.D.s with credentials showing that they hold valid license to practice medicine. (Membership card in C.M.A.; county medical society/association or A.M.A. membership card.) (b) Medical students will be admitted upon presentation of credentials from their medical schools identifying them as medical students. (A membership card of the Student American Medical Association or letter from their dean's office.) (c) Medical assistants will be admitted upon presentation of a letter from the physician-employer or C.M.A.A. membership card. (d) Military paramedical personnel will be admitted upon presentation of a letter requesting their admittance, written by their commanding officer. (e) Dentists (D.D.S.), doctors of veterinary medicine (D.V.M.), registered nurses (R.N.), student nurses, X-ray technicians, laboratory technicians, allied public health personnel, and others will be admitted provided they have proper identification. (f) *All questions on admission will be passed upon by a member of the Committee on Registration who will be present at the desk.*

ACKNOWLEDGMENT

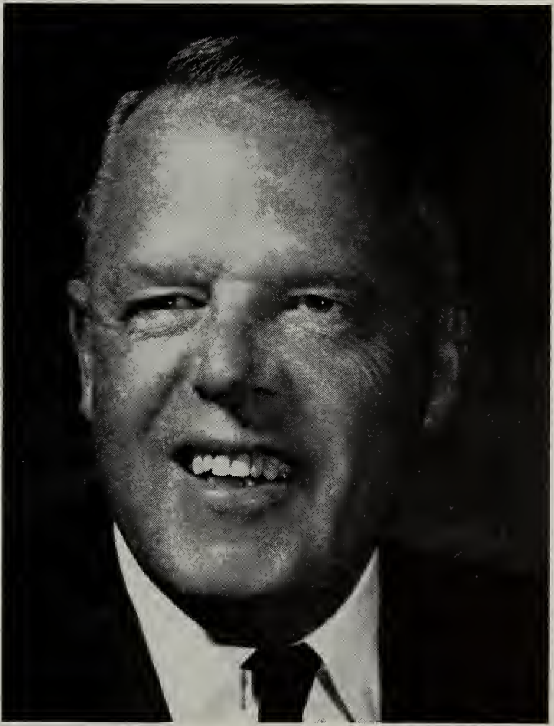
PLANNING AND HOLDING an Assembly as large and as complex as the Annual Meeting of the California Medical Association requires the assistance of over 30 program planners and over 300 speakers. The Committee on Scientific Assemblies appreciates their help, and thanks them on behalf of all the members of the California Medical Association. The Specialty Societies and Medical Schools in California have been increasingly helpful in recent years, and most of the improved quality of the programs is due to their work.

Committee on Scientific Assemblies
of the Scientific Board

JOHN B. DILLON, M.D., *Chairman*

CALIFORNIA MEDICAL ASSOCIATION

Malcolm C. Todd, *President*

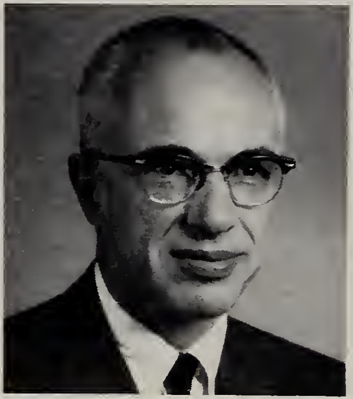


Albert G. Miller, *President-Elect*

Guest Speakers

ROBERT A. ALDRICH

ROBERT D. BLOODWELL


CLARK H. MILLIKAN

JOSEPH E. RALL

■ Robert A. Aldrich, M.D., Seattle—Professor and Head, Division of Human Ecology, Department of Pediatrics, School of Medicine; Director, Health Resources Study Center, University of Washington.

■ Robert D. Bloodwell, M.D., Houston—Assistant Professor of Surgery, Baylor University College of Medicine.

■ Barton Childs, M.D., Baltimore—Professor of Pediatrics, Johns Hopkins University, School of Medicine. (Not pictured.)

■ Clark H. Millikan, M.D., Rochester, Minn.—Senior Consultant, Department of Neurology, Mayo Clinic; Professor of Neurology, Mayo Graduate School of Medicine (University of Minnesota).

■ Joseph E. Rall, M.D., Ph.D., Bethesda, Md.—Director of Intramural Research, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health.

OUT-OF-STATE GUESTS OF SECTIONS AND ORGANIZATIONS

Anesthesiology

Alan W. Conn, M.D., Toronto, Ontario. Professor of Anesthesiology, University of Toronto.

Jay Jacoby, M.D., Philadelphia. Professor and Chairman, Department of Anesthesiology, Jefferson Medical College Hospital.

William W. Mushin, M.B., F.R.C.S., Cardiff, Wales. Professor of Anesthesia, Welsh National School of Medicine.

General Surgery

Lawrence Brettschneider, M.D., Denver. Assistant Professor of Surgery, University of Colorado Medical Center; Attending Physician and Director, Surgical Research Services, Veterans Administration Hospital.

Industrial Medicine

Eugene J. Ryan, M.D., Phoenix. Medical Director, Occupational Medical Services.

Internal Medicine

Arthur J. Seaman, M.D., Portland. Professor of Medicine, University of Oregon School of Medicine.

Pathology

Robert S. Lees, M.D., Cambridge. Associate Professor and Director, Clinical Research Center, Massachusetts Institute of Technology.

Preventive Medicine and Public Health

William A. Stewart, M.D., Washington, D.C. Principal Deputy to Assistant Secretary for Health and Scientific Affairs, Department of Health, Education and Welfare.

Radiology

J. Rosch, M.D., Prague, Czechoslovakia. Department of Radiology, Charles University.

California Medical Association,
American Cancer Society, Los Angeles County Branch
Cancer Symposium

Malin R. Dollinger, M.D., New York City. Clinical Assistant Physician, Medical Oncology Service, Memorial Hospital for Cancer and Allied Diseases; Instructor in Medicine, Cornell University Medical College.

Arthur I. Holleb, M.D., New York City. Senior Vice President for Medical Affairs, Chief Medical Office, American Cancer Society, Inc.; Consultant, Breast Service, Department of Surgery, Memorial Hospital for Cancer and Allied Diseases.

M. Vera Peters, M.D., Toronto, Ontario. Senior Radiotherapist, Ontario Cancer Institute, The Princess Margaret Hospital; Assistant Professor of Therapeutic Radiology, Faculty of Medicine, University of Toronto.

Jerome A. Urban, M.D., New York City. Associate Attending Surgeon, Breast Service, Memorial Hospital for Cancer and Allied Diseases; Clinical Professor of Surgery, Cornell University Medical College.

California Radiological Society
L. Henry Garland Memorial Lecture

Wendell G. Scott, M.D., St. Louis. Professor of Clinical Radiology, Washington University School of Medicine.

Committee on Cancer, California Medical Association

Richard J. Reed, M.D., New Orleans. Associate Professor of Pathology, Tulane University School of Medicine.

Council on Foods and Nutrition,
American Medical Association
Conference on Nutrition

Hugh R. Butt, M.D., Rochester. Professor of Internal Medicine and Chairman of the Section on Internal Medicine and Gastroenterology, Mayo Clinic, Mayo Graduate School of Medicine, University of Minnesota.

C. E. Butterworth, M.D., Birmingham. Professor of Medicine and Director of Nutrition, Department of Medicine, University of Alabama.

Wade Volwiler, M.D., Seattle. Professor of Medicine, Department of Gastroenterology, University of Washington.

special conferences

SATURDAY, MARCH 15 **9:30 a.m. to 5:00 p.m. —Colonial Room**

RADIOLOGY CONFERENCE

Committee on Cancer, California Medical Association

Chairman: Hooshang Taybi, M.D., Oakland
Secretary: G. M. McDonnel, M.D., Los Angeles

9:30 a.m. to 11:30 a.m.—THERAPY SESSION
1:30 p.m. to 3:30 p.m.—DIAGNOSTIC SESSION

SATURDAY, MARCH 15 **2:00 p.m. to 5:00 p.m. —Sheraton-Wilshire Motor Inn 3515 Wilshire Boulevard**

THIRD ANNUAL CANCER SYMPOSIUM

ADSCITITIOUS THERAPY ENHANCING SURVIVAL IN BREAST CANCER

Sponsored jointly by the California Medical Association and the Los Angeles County Branch of the American Cancer Society

Co-Moderators: Frederick W. George, M.D., Los Angeles, by invitation
James T. Helsper, M.D., Los Angeles

Members of the Panel: Jerome A. Urban, M.D., New York City, M. Vera Peters, M.D., Toronto, Arthur I. Holleb, M.D., New York City, and Malin R. Dollinger, M.D., New York City, all by invitation.

The primary management of breast cancer is generally accepted to be the standard radical mastectomy. However, the utilization of other specific and adjunctive therapies in the management of breast cancer has not been as clearly defined. Recent extensive reviews of breast cancer suggest the possibility of substantial improvement on existing survival rates. The panel participants will present from their own experience and that of others the improvement in survival and cure from the effects of various forms of adscititious therapy accompanying radical mastectomy.

Dr. Jerome A. Urban will briefly outline the principles of a standard radical mastectomy. This will be followed by his presentation of the accomplishments of the supraradical mastectomy and the internal mammary node dissection added to the standard radical mastectomy. The indications, as well as the results of this additional therapy will be presented.

Dr. M. Vera Peters will then present the results of her experience with radiation therapy alone, as well as pre-operative and post-operative radiation therapy combined with surgery. She will outline her views relative to the indications for these various therapeutic regimens.

Dr. Arthur I. Holleb will present his experience and that of others in the use of prophylactic oophorectomy, its indications and results, as well as therapeutic oophorectomy and therapeutic adrenalectomy, with the indications, response rates and end results.

Dr. Malin R. Dollinger will cover the subject of additive hormonal therapy. He will also present the indications for adjunct chemotherapy at the time of surgery, as well as the results thus far from a number of the national programs now being carried out. Dr. Dollinger will also discuss the indications for therapeutic chemotherapy in disseminated breast cancer, with its response rates.

SUNDAY, MARCH 16 **9:00 a.m. to 5:30 p.m. —Sheraton-Wilshire Motor Inn 3515 Wilshire Boulevard**

PATHOLOGY CONFERENCE

Committee on Cancer, California Medical Association

Tumors of the Skin

Chairman: David D. Rulon, Capt., MC, USN, Oakland, by invitation

Moderator: Richard J. Reed, M.D., New Orleans, by invitation

9:00 a.m. to 12:30 p.m.—2:00 p.m. to 5:30 p.m.

Those who wish slides and protocols for the Conference (cost, $25.00) are requested to register with Weldon K. Bullock, M.D., Registrar, Tumor Tissue Registry, CMA Committee on Cancer, Los Angeles County Hospital, 1200 North State Street, Los Angeles, 90033. The $25.00 fee includes registration. For those who wish to attend the Conference, the fee is $25.00. There is no charge for residents and interns.

SUNDAY, MARCH 16 **2:00 p.m.—Colonial Room**

Third Annual
L. HENRY GARLAND MEMORIAL LECTURE

Sponsored by the California Radiological Society

2:00—**Introduction**—G. Melvin Stevens, M.D., Palo Alto, President, California Radiological Society.

2:05—**New Concepts in Cancer Control—Preventable and Avoidable Cancers**—Wendell G. Scott, M.D., St. Louis, by invitation.

3:00—**Recess.**

3:15—**Annual Meeting—California Radiological Society.**

MONDAY, MARCH 17 **9:00 a.m.—The Lautrec**

EMERGENCY MEDICAL SERVICES

Symposium

Committee on Automotive and Traffic Safety,
Committee on Disaster Medical Care, and
Committee on Emergency Medical Care,
California Medical Association

Chairman: Thomas W. Lyons, M.D., La Mesa

9:00—**Opening Remarks and Orientation**—Marvin J. Shapiro, M.D., Encino.

9:15—**The Challenge to Provide Emergency Services**

PANEL DISCUSSION

Moderator: Thomas W. Lyons, M.D., La Mesa

1. **San Diego County**—Stephen Murphy, M.D., San Diego.
2. **San Francisco System**—John Heald, M.D., San Francisco.
3. **Rural Program**—Speaker to be announced.

10:15—**Question and Answer Period.**

10:45—**Break.**

11:00—**Preparation, Care and Transport of the Casualty**

PANEL DISCUSSION

Moderator: Wayne P. Chesbro, M.D., Berkeley

1. **California Highway Patrol**—Inspector E. D. Heringer, Los Angeles, by invitation.
2. **California Ambulance Association**—Bruno Bakey, Los Angeles, by invitation.
3. **San Diego Fire Department**—Speaker to be announced.

12:00—**Question and Answer Period.**

MONDAY, MARCH 17 **2:00 p.m.—The Lautrec**

Symposium on Emergency Medical Services

(Continued)

2:00—**The Emergency Room**

PANEL DISCUSSION

Moderator: Carl E. Anderson, M.D., Santa Rosa

1. **San Francisco, Regional First Aid Station**—John Heald, M.D., San Francisco.
2. **Los Angeles (Megalopolis), Central Receiving Plan**—Walter Ellerbeck, M.D., Los Angeles.
3. **San Diego, Coordination and Rating of Private Facilities**—Stephen Murphy, M.D., San Diego.
4. **Rural City-County Emergency Plan**—Speaker to be announced.

3:15—**Panel Discussion.**

3:30—**Question and Answer Period.**

MONDAY, MARCH 17 **9:00 a.m.—East Venetian Room**

FAMILY LIFE EDUCATION

The Role of the Physician and Clergyman

Committee on Medicine and Religion and
Committee on School and College Health,
California Medical Association

Co-Chairmen: Albert E. Long, M.D., Daly City
Tom W. Robinson, M.D., Newport Beach

9:00—**Situation Today: Schools**—Wilfred Sutton, Ed.D., Northridge, by invitation.

9:30—**Situation Today: Medicine**—Harriett B. Randall, M.D., Los Angeles.

10:00—**Situation Today: Church**—Melvin E. Wheatley, Jr., D.D., Los Angeles, by invitation.

10:45—**Panel Discussion**—Question and Answer Period.

MONDAY, MARCH 17 **2:00 p.m.—East Venetian Room**

Family Life Education (Continued)

2:00—**How Can Doctors Work in the Schools?**—Wilfred Sutton, Ed.D., Northridge, by invitation.

2:30—**How Can the Clergyman Work in the Schools?**—Melvin E. Wheatley, Jr., D.D., Los Angeles, by invitation.

3:00—**How Can the Doctor and the Clergyman Work in the Schools?**—Harriett B. Randall, M.D., Los Angeles.

3:30—**How Medical Students are Working in the Schools in San Francisco**—James Tappan, A.B., San Francisco, by invitation.

4:00—**Panel Discussion**—Question and Answer Period.

MONDAY, MARCH 17 **2:00 p.m.—Sheraton-Wilshire Motor Inn, 3515 Wilshire Boulevard**

CONFERENCE ON NUTRITION

Council on Foods and Nutrition, American Medical Association

Chairman: Hugh R. Butt, M.D., Rochester, Minn., by invitation.

2:00—**Chairman's Opening Remarks**—Hugh R. Butt, M.D., Rochester, Minn., by invitation.

2:20—**Dietary and Environmental Influences on Intestinal Gas Formations**—Doris Calloway, Ph.D., Berkeley, by invitation.

2:50—**Break.**

3:00—**Dietary Considerations in Treating Gastrointestinal Disease**—Wade Volwiler, M.D., Seattle, by invitation.

3:30—**Malabsorption Syndromes—Diagnosis and Management**—C. E. Butterworth, M.D., Birmingham, Ala., by invitation.

4:00—**Questions and Answers**—Panel Discussion.

TUESDAY, MARCH 18 **10:00 a.m.—Regency Room**

YOUR MEDICAL ASSISTANT— PEARL OR PASTE?

California Medical Assistants Association

Chairman: Grace Nix, C.M.A.A., Anaheim

A Special Conference for the Physician to Help Improve His Relationship with His Office Personnel

10:00—**Introductions**—Grace Nix, C.M.A.A., Anaheim.

1. **Culturing: How She Is Trained**—Dorothy Buckley, C.M.A.A., Fullerton — Educator, Fullerton Junior College.
2. **Finding: How You Can Get One**—Patricia Griswold, Santa Ana — Medical Employment Representative.
3. **Polishing: How She Keeps Up-to-Date**—Betty Massey, C.M.A.A., Chula Vista—National Trustee for A.A.M.A.
4. **Treasuring: How She Makes or Breaks You**—Patricia Hampton, Los Angeles — Secretary, Children's Hospital, Los Angeles.
5. **Insuring: How You Can Keep One** — Frances Davis, C.M.A.A., Laguna Beach — Medical Secretary.
6. **Admiring: How About It?**—Edgar R. Palarea, M.D., Long Beach — Advisor to C.M.A.A.

WEDNESDAY, MARCH 19 **9:00 a.m.—Colonial Room**

TREATMENT AND PREVENTION OF SELF-INFLICTED DRUG OVERDOSE

Symposium

Committee on Adverse Drug Reactions, California Medical Association

Moderator: Ronald Okun, M.D., Los Angeles

9:00—**Introduction**—Ronald Okun, M.D., Los Angeles.

9:10—**Diuresis and Diarrhea in Downers***—Alan G. Silverman, M.D., Los Angeles.

9:50—**Dialyzing Out the Downers***—Arthur Gordon, M.D., Los Angeles.

10:30—**The Suicide Attempt**—Donald H. Naftulin, M.D., Los Angeles.

11:10—**Summary**—Ronald Okun, M.D., Los Angeles.

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*Persons taking an excess of depressant drugs such as barbiturates.

Scientific Sessions

GENERAL MEETINGS

FIRST GENERAL MEETING

SUNDAY, MARCH 16 **2:30 p.m.—Cocoanut Grove**

Symposium on Stroke

Moderator: Vernon L. Nickel, M.D., Downey

2:30—**Introduction**—Vernon L. Nickel, M.D., Downey.

2:40—**Diagnostic Procedures in Stroke (Medical and Neurological)**—Clark H. Millikan, M.D., Rochester, Minn., by invitation.

3:00—**Diagnostic Procedures and Vascular Surgery in Stroke Patients**—Robert D. Bloodwell, M.D., Houston, by invitation.

3:20—**Physical Treatment for Post-acute Stroke Patients, Including Nursing, Physical and Occupational Therapy**—Walter J. Treanor, M.D., San Francisco.

3:40—**Peripheral Surgery and Control of Spasticity in Stroke Patients**—Vert Mooney, M.D., San Francisco.

4:00—**The Stroke Team Concept as Implemented by Regional Medical Programs** — B. L. Tesman, M.D., Anaheim.

4:20—**Inter-Panel Discussion and Question and Answer Period.**

SECOND GENERAL MEETING

MONDAY, MARCH 17 **2:00 p.m.—Cocoanut Grove**

A Physiologic Basis of Metabolic Disease

Moderator: Carl M. McCandless, M.D., San Francisco

2:00—**Introductory Remarks**—Carl M. McCandless, M.D., San Francisco.

2:05—**Metabolic Derangements in Thyroid Biochemistry and Their Clinical Consequences**—Joseph E. Rall, M.D., Ph.D., Bethesda, Md., by invitation.

2:35—**Recent Advances in Reproductive Physiology**—William Odell, M.D., Torrance, by invitation.

3:00—**Recess.**

3:15—**Physiologic Basis of Congestive Heart Failure**—Eugene Braunwald, M.D., La Jolla, by invitation.

3:40—**Purine Metabolism and Gout**—James Klinenberg, M.D., Los Angeles, by invitation.

4:05—**Hyperuricemia as Found by Screenings—Its Clinical Significance**—Harold Paulus, M.D., Los Angeles, by invitation.

4:30—**Questions.**

THIRD GENERAL MEETING

TUESDAY, MARCH 18 **9:30 a.m.—Cocoanut Grove**

The Damaged Child: What Is His Inheritance?

Moderator: Lester T. Hibbard, M.D., Los Angeles

9:30—**Neonatal Manifestations of Maternal Disease**—Joan E. Hodgman, M.D., Los Angeles.

10:00—**Counselling the Parents of the Defective Child**—Richard Koch, M.D., Los Angeles.

10:30—**Newborn Errors of Metabolism**—Barton Childs, M.D., Baltimore, by invitation.

11:15—**Public Policy and the Malformed Child**—Robert A. Aldrich, M.D., Seattle, by invitation.

12:00—**Questions and Answers.**

SECTION MEETINGS

ALLERGY

Chairman..........Samuel Ross, m.d., Fresno
Secretary..........Bailey J. Lovin, Jr., m.d., Reseda
Assistant Secretary..........E. James Young, m.d., San Mateo

SUNDAY, MARCH 16 — 9:00 a.m.—Oval Suite A

9:00—**Blood Levels Following Intravenous Aminophylline**—Walter R. MacLaren, M.D., Pasadena.

9:30—**Office Spirometry and Pulmonary Function Studies**—Max Benis, M.D., Sherman Oaks, and Daniel Wiseman, M.D., Los Angeles, by invitation.

10:20—**Recess.**

10:40—**Right Middle Lobe Syndrome** — Paul Ququndab, M.D., Irvine, by invitation.

11:10—**Airway Responses to Air Pollutants**—Stanley N. Rokaw, M.D., Irvine.

SUNDAY, MARCH 16 — 12:00 noon—Oval Suite A

12:00—**Luncheon and Business Meeting with the California Society of Allergy.**

ANESTHESIOLOGY

Chairman..........Donald A. Walker, m.d., Tiburon
Secretary..........Hamilton S. Davis, m.d., Davis
Assistant Secretary..........Edward B. Scott, m.d., Los Angeles

SUNDAY, MARCH 16 — 9:00 a.m.—Dolphin Court

9:00—**Coordination of Meeting** — Introductory remarks and room assignments. A number of informal round table discussions are planned. There will be two co-chairmen at each table and 6-8 seats for participating audience. Cards will label lead topics for each table. Discussion periods will be one hour each.

9:30—**Round Table Discussions**—To be held in rooms assigned at 9:00 a.m.

Round Table Co-Chairmen:
Verne L. Brechner, M.D., Los Angeles
David D. Cohen, M.D., Los Angeles
Alan W. Conn, M.D., Toronto, Canada, by invitation
Harold L. Engel, M.D., Studio City
Ernest P. Guy, M.D., San Francisco
William K. Hamilton, M.D., San Francisco, by invitation
John S. Hattox, Jr., M.D., San Diego
Jay Jacoby, M.D., Philadelphia, by invitation
Jordan Katz, M.D., Palo Alto
Gilbert E. Kinyon, M.D., La Jolla
George B. Lewis, Jr., M.D., Los Angeles
Milton J. Marmer, M.D., Beverly Hills
Edwin S. Munson, M.D., Davis, by invitation
William W. Mushin, M.B., F.R.C.S., Cardiff, Wales, by invitation
Joseph Riggio, Jr., M.D., Northridge
Morley M. Singer, M.D., San Francisco
Robert H. Smith, M.D., San Francisco

SUNDAY, MARCH 16 — 1:30 p.m.—Dolphin Court

1:30— **Temperature Aberrations During Anesthesia**

Panel Discussion

Moderator: Hamilton S. Davis, M.D., Davis

Members of the Panel: Alan W. Conn, M.D., Toronto, Canada, by invitation; Loren Carlson, Ph.D., Davis, by invitation; M. Digby Leigh, M.D., Los Angeles; and William W. Mushin, M.B., F.R.C.S., Cardiff, Wales, by invitation.

3:15—**Final Round Tables.**

4:15—**Business Meeting.**

DERMATOLOGY

Chairman..........George T. Wilson, m.d., Palo Alto
Secretary..........Charles G. Steffen, m.d., Covina
Assistant Secretary....Harold M. Schneidman, m.d., San Francisco

SATURDAY, MARCH 15 — 2:00 p.m.—Hoffman Building, University of Southern California School of Medicine, Zonal Avenue (Adjacent to USC-Los Angeles County General Hospital), Los Angeles

Pre-Convention Meeting

There will be a clinical meeting of the combined Los Angeles and Metropolitan Dermatological Societies at 2:00 p.m. The program will consist of presentation of cases, followed by discussion, and will continue until 4:30 p.m. Round-trip bus transportation will be provided, leaving the Ambassador Hotel at 1:30 p.m.

The program will be followed at 6:30 p.m. by a no-host cocktail party and dinner at the Music Center, 135 North Grand. Dress is dark suit, and reservations at $10.00 per person may be made by sending a check to: Margaret Ann Storkan, M.D., Secretary, Los Angeles Dermatological Society, 217 Avenida del Norte, Redondo Beach, California 90277. All dermatologists are invited by the Los Angeles and Metropolitan Dermatological Societies to attend.

SUNDAY, MARCH 16 — 8:30 a.m.—East Venetian Room

Controversial Areas in Therapy

Round Table Discussions

8:30— First Session

Moderator: Harold M. Schneidman, M.D., San Francisco

1. **Anti-malarials in Skin Diseases**—Denny L. Tuffanelli, M.D., San Francisco.

2. **Systemic Steroids in Atopic Dermatitis**—Marion B. Sulzberger, M.D., San Francisco, by invitation.
3. **Methotrexate in Psoriasis**—Rees B. Rees, Jr., M.D., San Francisco.
4. **Therapy of Psoriasis**—Eugene M. Farber, M.D., Palo Alto.
5. **Management of Atopic Dermatitis** — Jud R. Scholtz, M.D., Palo Alto.

9:30—**Recess.**

9:45— SECOND SESSION

Moderator: George T. Wilson, M.D., Palo Alto

1. **Surgery in Skin Cancer** — Ralph H. Luikart II, M.D., Santa Barbara.
2. **Radiotherapy in Skin Cancer**—Paul M. Crossland, M.D., Santa Rosa.
3. **5-Fluorouracil in Skin Tumors**—Robert B. Pappenfort, M.D., San Diego.
4. **Treatment of Keratoacanthoma** — Walter R. Nickel, M.D., San Diego.
5. **Treatment of Moles** — Robert G. Walton, M.D., Modesto.

10:45—**Recess.**

11:00— THIRD SESSION

Moderator: Victor D. Newcomer, M.D., Los Angeles

1. **Treatment of Superficial Fungus Infections** — J. Walter Wilson, M.D., Long Beach, by invitation.
2. **Treatment of Acne** — Ronald M. Reisner, M.D., Los Angeles.
3. **Steroids and Antibiotics in Acne** — Marjorie Frantz Bauer, M.D., Los Angeles.
4. **Hormonal Treatment of Acne** — Donald G. Lindsay, M.D., Ventura.
5. **Hyposensitization in Skin Diseases** — Julian L. Harwell, M.D., Pasadena.

12:00—**Business Meeting.**

GENERAL PRACTICE

Chairman..........................ALLEN F. STERLING, M.D., SAN BERNARDINO
Secretary.......................................ROBERT F. GOBAR, M.D., DALY CITY
Assistant Secretary....CLARENCE W. BURRILL, JR., M.D., WESTMINSTER

MONDAY, MARCH 17 9:30 a.m.—Colonial Room

Combined Meeting with Sections on Pediatrics and Obstetrics and Gynecology

Chairman: Robert J. Harvey, M.D., San Francisco

9:30—**Genetic Counselling**—Barton Childs, M.D., Baltimore, by invitation.

10:15—**Pediatric Gynecology**—Robert A. Sack, M.D., Los Angeles.

11:00—**Recess.**

11:20—**Question and Answer Period.**

12:00—**Business Meeting**—General Practice.

MONDAY, MARCH 17 12:00 noon—Dolphin Court

12:00—**Joint Luncheon Meeting with the California Division of the American College of Obstetricians and Gynecologists.**

Luncheon Address: Basic Science and the Obstetrician—Lawrence D. Longo, M.D., Loma Linda, by invitation.

Advance reservations may be made by contacting James C. Caillouette, M.D., 123 Congress Street, Pasadena 91105, (213) 796-7145.

MONDAY, MARCH 17 2:00 p.m.—Colonial Room

Combined Meeting with Section on Obstetrics and Gynecology

2:00— **Therapeutic Abortion in California**

PANEL DISCUSSION

Moderator: James W. Ravenscroft, M.D., San Diego

Members of the Panel: Keith P. Russell, M.D., Los Angeles; Theodore Montgomery, M.D., Berkeley; Catherine Cline Pike, M.D., Ross; Mr. Frank R. McDougall, Vice-President, Lutheran Hospital Society of Southern California, Los Angeles, by invitation; Mr. James Don Keller, District Attorney, San Diego County, by invitation; and Mr. William Weitekamp, Area Administrator, Unit II, Los Angeles County-University of Southern California Medical Center, by invitation.

3:00—**Question and Answer Period.**

3:30—**Recess.**

3:35—**Business Meeting**—Obstetrics and Gynecology.

TUESDAY, MARCH 18 1:00 p.m.—Colonial Room

Combined Meeting with Section on Pediatrics
Co-Sponsored by the American Academy of Pediatrics, Chapter II, and the Southwest Pediatric Society

1:00— **Learning Disorders**

SYMPOSIUM

Moderator: Robert J. Harvey, M.D., San Francisco

1:00—**Learning Disorders as a School Health Problem: A General Strategy** — Robert A. Aldrich, M.D., Seattle, by invitation.

1:20—**Learning Disorders as a School Health Problem: Pediatric Aspects** — Helen F. Gofman, M.D., San Francisco, by invitation.

1:40—**Neurological Examination of Higher Cerebral Function in Children with Learning Disorders**—Robert Sedgwick, M.D., Los Angeles.

2:00—**Learning Disorders as a School Health Problem: Neurological and Psychiatric Aspects** — Leon J. Whitsell, M.D., San Francisco.

2:20—**Learning Disorders as a School Health Problem: Auditory and Linguistic Aspects** — Richard M. Flower, Ph.D., San Francisco, by invitation.

2:40—**Learning Disorders as a School Health Problem: Educational Aspects**—Alice J. Whitsell, A.B., San Francisco, by invitation.

3:00—**Recess.**

(Continued on next page)

3:20—

Medical Management of Learning Disorders

Panel Discussion

Moderator: Kenneth Z. Zike, M.D., Torrance

Members of the Panel: Participants as listed above.

4:00—The Shodding of Children: Sham or Science? —Eugene E. Bleck, M.D., San Mateo.

4:20—Business Meeting—Pediatrics.

GENERAL SURGERY

Chairman	Robert T. Hood, Jr., m.d., Van Nuys
Secretary	Harold H. Lindner, m.d., San Francisco
Assistant Secretary	James W. Martin, m.d., Sacramento

TUESDAY, MARCH 18 9:00 a.m.—East Venetian Room

9:00—

Organ Transplantation

Symposium

Moderator: Robert T. Hood, Jr., M.D., Van Nuys

9:00—Heart Transplants — Eugene Dong, Jr., M.D., Palo Alto, by invitation.

9:30—Liver Transplants—Lawrence Brettschneider, M.D., Denver, by invitation.

10:00—Kidney Transplants—Thomas V. Berne, M.D., Los Angeles.

10:30—Immunology of Organ Transplantation — Victor Richards, M.D. San Francisco.

11:00—Round Table Discussion by Panel. Microphones will be set up throughout the auditorium so that the audience may ask questions.

TUESDAY, MARCH 18 1:30 p.m.—East Venetian Room

1:30—Business Meeting.

1:45—The Surgical Treatment of Obesity — J. Howard Payne, M.D., Los Angeles.

2:15—Palliative Treatment of Advanced Mammary Cancer—Arthur J. Donovan, M.D., Pasadena.

2:45—Newer Tests for Evaluation of Thyroid Function—Joseph E. Rall, M.D., Ph.D., Bethesda, Md., by invitation.

3:15—Preparation of the Diabetic Patient for Surgery—Leona Miller, M.D., Los Angeles, by invitation.

3:30—Chairman's Address: Cholecystectomy and Cholecystostomy: Clinical Study—Robert T. Hood, Jr., M.D., Van Nuys.

INDUSTRIAL MEDICINE AND SURGERY

Chairman	James G. Forgerson, m.d., San Francisco
Secretary	David P. Discher, m.d., Los Angeles
Assistant Secretary	Walter J. Gillogley, m.d., Sunnyvale

MONDAY, MARCH 17 9:30 a.m.—Sheraton-Wilshire Motor Inn, 3515 Wilshire Boulevard

9:30—New Clinical Tools for the Occupational Physician —E. J. Ryan, M.D., Phoenix, by invitation.

10:00—Surgical and Rehabilitative Tools Needed in Occupational Medicine—Robert C. Combs, M.D., Irvine.

10:30—Pointers for Providing Medical Services to Insurance Carriers—Herbert J. Kirchner, M.D., Los Angeles.

11:00—

"State of the Art" in Occupational Disease Diagnosis

Panel Discussion

Moderator: Jean S. Felton, M.D., Los Angeles, by invitation.

Members of the Panel: Henry G. Morgan, M.D., and George Schwartz, M.D., Los Angeles; and Walter J. Gillogley, M.D., Sunnyvale.

11:45—Business Meeting.

INTERNAL MEDICINE

Chairman	Leyland E. Stevens, m.d., San Francisco
Secretary	Pettus G. Secrest, m.d., Long Beach
Assistant Secretary	M. Glenn Molyneaux, m.d., San Francisco

SUNDAY, MARCH 16 9:15 a.m.—Cocoanut Grove

Presented by the Department of Medicine, University of California, Los Angeles

9:15—

Hematology

Chairman: William N. Valentine, M.D., Professor and Chairman, Department of Medicine, University of California, Los Angeles

9:15—The Diagnosis and Management of Hodgkin's Disease — Current Concepts — David L. Rosenbaum, M.D., Los Angeles.

9:45—The Hereditary Hemolytic Anemia Associated with Erythrocyte Enzyme Deficiencies — Arthur S. Schneider, M.D., Duarte.

10:15—Recess.

10:30—The Auto-immune Aspects of Pernicious Anemia—Leonard Goldberg, M.D., Los Angeles, by invitation.

11:00—Viruses and Leukemia—Esther F. Hays, M.D., Los Angeles, by invitation.

11:30—Multiple Myeloma, Diagnosis and Management—Current Concepts—William A. Skoog, M.D., Los Angeles.

MONDAY, MARCH 17 9:00 a.m.—Cocoanut Grove

Presented Jointly by the Section on Internal Medicine and University of Southern California School of Medicine

9:00—

Disorders of Hemostasis

Chairman: Thomas H. Brem, M.D., South Pasadena

9:00—The Rapid Screening Evaluation of a Patient with a Suspected Bleeding Disorder — Samuel I. Rapaport, M.D., Los Angeles.

9:40—**Newer Approaches to the Management of Hemophilia**—Carol K. Kasper, M.D., Los Angeles, by invitation.

10:05—**Bleeding Disorders Complicating Immunologic Disease**—Donald I. Feinstein, M.D., Los Angeles, by invitation.

10:35—**Recess.**

10:45—**Thrombotic Thrombocytopenic Purpura**—C. Garnett Massey, M.D., Los Angeles, by invitation.

1:15—**The Therapeutic Use of Anticoagulants**—Arthur J. Seaman, M.D., Portland, by invitation.

TUESDAY, MARCH 18 — 2:00 p.m.—Cocoanut Grove

Presented Jointly by the Section on Internal Medicine and The American College of Cardiology

Co-Moderators: J. Douglas McNair, M.D., Arcadia
John J. Sampson, M.D., San Francisco

2:00—**Prevention of Strokes**—Clark H. Millikan, M.D., Rochester, Minn., by invitation.

2:35—**Newer Trends in Treatment of Angina Pectoris**—Dean T. Mason, M.D., Davis, by invitation.

3:10—**Recess.**

3:25—**Problems in Management of Acute Myocardial Infarction in the Coronary Care Unit**—Elliot Rapaport, M.D., San Francisco.

4:00—**Human Cardiac Transplantation**—Robert D. Bloodwell, M.D., Houston, by invitation.

4:45—**Colloquia with Afternoon Lecturers** (Followed by Business Meeting).

OBSTETRICS AND GYNECOLOGY

Chairman	James W. Ravenscroft, m.d., San Diego
Secretary	Clifford C. Chappell, m.d., Berkeley
Assistant Secretary	James C. Caillouette, m.d., Pasadena

MONDAY, MARCH 17 — 9:30 a.m.—Colonial Room

Combined Meeting with Sections on General Practice and Pediatrics

Chairman: Robert J. Harvey, M.D., San Francisco

9:30—**Genetic Counselling**—Barton Childs, M.D., Baltimore, by invitation.

10:15—**Pediatric Gynecology**—Robert A. Sack, M.D., Los Angeles.

11:00—**Recess.**

11:20—**Question and Answer Period.**

12:00—**Business Meeting**—General Practice.

MONDAY, MARCH 17 — 12:00 noon—Dolphin Court

12:00—**Joint Luncheon Meeting with the California Division of the American College of Obstetricians and Gynecologists.**

Luncheon Address: Basic Science and the Obstetrician—Lawrence D. Longo, M.D., Loma Linda, by invitation.

Advance reservations may be made by contacting James C. Caillouette, M.D., 123 Congress Street, Pasadena 91105, (213) 796-7145.

MONDAY, MARCH 17 — 2:00 p.m.—Colonial Room

Combined Meeting with Section on General Practice

2:00— **Therapeutic Abortion in California**

Panel Discussion

Moderator: James W. Ravenscroft, M.D., San Diego

Members of the Panel: Keith P. Russell, M.D., Los Angeles; Theodore Montgomery, M.D., Berkeley; Catherine Cline Pike, M.D., Ross; Mr. Frank R. McDougall, Vice-President, Lutheran Hospital Society of Southern California, Los Angeles, by invitation; Mr. James Don Keller, District Attorney, San Diego County, by invitation; and Mr. William Weitekamp, Area Administrator, Unit II, Los Angeles County-University of Southern California Medical Center, by invitation.

3:00—**Question and Answer Period.**

3:30—**Recess.**

3:35—**Business Meeting**—Obstetrics and Gynecology.

OPHTHALMOLOGY

Chairman	Robert E. Hopkins, m.d., Stockton
Secretary	J. P. McBride, m.d., Los Angeles
Assistant Secretary	Theodore Steinberg, m.d., Fresno

SUNDAY, MARCH 16 — 2:00 p.m.—Coral Room
Gaylord Hotel, 3355 Wilshire Boulevard
(Opposite Ambassador Hotel)

Chairman: Robert E. Hopkins, M.D., Stockton

2:00—**Automobile Injuries of the Orbit**—Orwyn H. Ellis, M.D., Los Angeles.

2:30—**The Eye as a Target Organ in Cerebrovascular Disease**—Irvin M. Kalb, M.D., Los Angeles.

3:30—**Ocular Findings in Metabolic Disease**—Warren A. Wilson, M.D., Los Angeles.

3:30—**Observations on Disorders of Macula**—Thomas H. Pettit, M.D., Los Angeles.

4:00—**Business Meeting.**

ORTHOPEDICS

Chairman..................................Vernon L. Smythe, m.d., Los Angeles
Secretary...John A. Blosser, m.d., Oakland
Assistant Secretary..............Chadwick F. Smith, m.d., Los Angeles

SUNDAY, MARCH 16 9:15 a.m.—Gold Room

The Patient with Back Pain —A Conservative Approach

Round Table Conference

Moderator: Vernon L. Smythe, M.D., Los Angeles

> **Following each presentation there will be a brief discussion period. Microphones will be available. Audience participation is welcome.**

1. **Opening Remarks—A Symptom Not a Specific Disease**—Vernon L. Smythe, M.D., Los Angeles.
2. **Anatomy and Physiology of the Spine**—Vernon L. Smythe, M.D., Los Angeles.
3. **Biomechanics of the Back**—Leon Lamont Wiltse, M.D., Long Beach.
4. **Consideration of the Whole Patient With Back Pain**—John A. Blosser, M.D., Oakland.
5. **Conservative Management of the Patient With Back Pain**—Thomas Gucker, M.D., Los Angeles.
6. **The Social, Emotional and Economic Aspects of the Patient With Low Back Pain** — J. Vernon Luck, M.D., Los Angeles.
7. **The Conservative Surgeon Looks at Back Pain**—Douglas D. Dickson, M.D., Oakland.

12:15—**Business Meeting.**

OTOLARYNGOLOGY

Chairman.......................................Irving L. White, m.d., Long Beach
Secretary..Emile Gough, m.d., Stockton
Assistant Secretary.............Edward A. Kantor, m.d., Beverly Hills

SUNDAY, MARCH 16 9:30 a.m.—Regency Room

Chairman: Irving L. White, M.D., Long Beach

9:30—**Rinkle Titration Technique in Management of Ear, Nose and Throat Allergy Problems** — Thomas L. Soss, M.D., San Mateo.

10:00—**Sublingual Desmoids**—Alfred D. Katz, M.D., and Victor Passey, M.D., Los Angeles.

10:30—**Noise-Induced Hearing Loss: Some Small Arms Fire**—Robert J. Keim, M.D., Los Angeles.

11:00—**Background and Current Status, Assembly Bill 1425**—Mansfield F. W. Smith, M.D., San Jose.

11:30—**Diagnosis and Management of Facial Paralysis**—Ronald Strahan, M.D., Torrance, by invitation; and Richard E. Katz, M.D., Garden Grove.

PATHOLOGY

Chairman............................Donald L. Bittner, m.d., San Francisco
Secretary...Jerome L. Heard, m.d., San Diego
Assistant Secretary...........................Osman H. Hull, m.d., Monterey

SATURDAY, MARCH 15 9:00 a.m.—Sheraton-Wilshire Motor Inn, 3515 Wilshire Boulevard

Lipids and Triglycerides

9:00—**Newer Methods in the Diagnosis of Hyperlipidemia**—Robert S. Lees, M.D., Cambridge, Mass., by invitation.

9:45—**Break.**

10:00—**Triglycerides and Cholesterol: Screening and Clinical Correlation**—Bernard J. Poletti, M.D., and Robert F. Hufner, M.D., Los Angeles.

10:30—**Lipoprotein Electrophoresis in Thin Agarose Gel**—Franklin R. Elevitch, M.D., San Francisco.

11:00—**Screening for Alterations in Lipids and Related Parameters on Routine Hospital Admissions** — Samuel T. Nerenberg, M.D., Ph.D., San Francisco.

11:30—**Separation and Quantitation of Lipid Particles in Serum by Filtration**—Mario Werner, M.D., San Francisco, by invitation.

SATURDAY, MARCH 15 1:30 p.m.—Sheraton-Wilshire Motor Inn, 3515 Wilshire Boulevard

1:30—**Business Meeting** — Pathology Section, California Medical Association and California Society of Pathologists.

SUNDAY, MARCH 16 9:00 a.m.-5:30 p.m.—Sheraton-Wilshire Motor Inn, 3515 Wilshire Boulevard

PATHOLOGY CONFERENCE

Tumors of the Skin

Committee on Cancer, California Medical Association

Chairman: David D. Rulon, Capt., MC, USN, Oakland, by invitation.

Moderator: Richard J. Reed, M.D., New Orleans, by invitation.

9:00 a.m. to 12:30 p.m.—2:00 p.m. to 5:30 p.m.

Those who wish slides and protocols for the Conference (cost, $25.00) are requested to register with Weldon K. Bullock, M.D., Registrar, Tumor Tissue Registry, CMA Committee on Cancer, Los Angeles County Hospital, 1200 North State Street, Los Angeles, 90033. The $25.00 fee includes registration. For those who wish to attend the Conference, the fee is $25.00. There is no charge for residents and interns.

PEDIATRICS

Chairman............................Robert J. Harvey, m.d., San Francisco
Secretary..Eugene Gettelman, m.d., Encino
Assistant Secretary.....................Isaac M. Reid, m.d., San Francisco

MONDAY, MARCH 17 9:30 a.m.—Colonial Room

Combined Meeting with Sections on General Practice and Obstetrics and Gynecology

Chairman: Robert J. Harvey, M.D., San Francisco

9:30—**Genetic Counselling**—Barton Childs, M.D., Baltimore, by invitation.

10:15—**Pediatric Gynecology**—Robert A. Sack, M.D., Los Angeles.

11:00—**Recess.**

11:20—**Question and Answer Period.**

12:00—**Business Meeting**—General Practice.

TUESDAY, MARCH 18 11:30 a.m.—Colonial Room

11:30—**Luncheon with the American Academy of Pediatrics—Chapter II, District IX.**

Luncheon Address: New Directions for Pediatricians—Dan Moore, Special Assistant to the Publisher of the *Los Angeles Times,* by invitation.

Advance reservations are necessary, and may be made with Eve Black, P.O. Box 2134, Inglewood 90305, (213) 753-3704.

TUESDAY, MARCH 18 1:00 p.m.—Colonial Room

Combined Meeting with Section on General Practice Co-Sponsored by the American Academy of Pediatrics, Chapter II, and the Southwest Pediatric Society

1:00— **Learning Disorders**

Symposium

Moderator: Robert J. Harvey, M.D., San Francisco

1:00—**Learning Disorders as a School Health Problem: A General Strategy**—Robert A. Aldrich, M.D., Seattle, by invitation.

1:20—**Learning Disorders as a School Health Problem: Pediatric Aspects**—Helen F. Gofman, M.D., San Francisco, by invitation.

1:40—**Neurological Examination of Higher Cerebral Function in Children with Learning Disorders**—Robert Sedgwick, M.D., Los Angeles.

2:00—**Learning Disorders as a School Health Problem: Neurological and Psychiatric Aspects** — Leon J. Whitsell, M.D., San Francisco.

2:20—**Learning Disorders as a School Health Problem: Auditory and Linguistic Aspects**—Richard M. Flower, Ph.D., San Francisco, by invitation.

2:40—**Learning Disorders as a School Health Problem: Educational Aspects**—Alice J. Whitsell, A.B., San Francisco, by invitation.

3:00—**Recess.**

3:20— **Medical Management of Learning Disorders**

Panel Discussion

Moderator: Kenneth Z. Zike, M.D., Torrance

Members of the Panel: Participants as listed above.

4:00—**The Shodding of Children: Sham or Science?** — Eugene E. Bleck, M.D., San Mateo.

4:20—**Business Meeting**—Pediatrics.

PHYSICAL MEDICINE AND REHABILITATION

Chairman.................................Elizabeth Austin, m.d., Los Angeles
Secretary.......................S. Malvern Dorinson, m.d., San Francisco
Assistant Secretary.......................Jesse A. Bowers, m.d., San Diego

MONDAY, MARCH 17 9:00 a.m.—Wilshire Room

Pain in Neuromuscular Skeletal Conditions

First Session

Moderator: S. Malvern Dorinson, M.D., San Francisco

9:00—**Foot Pain—Evaluation and Treatment**—Rene Cailliet, M.D., Los Angeles.

9:50—**Recess.**

10:00—**Low Back Pain—Evaluation and Treatment**—David Rubin, M.D., Los Angeles.

10:50—**Recess.**

11:15—**Neck Pain—Evaluation and Treatment**—Lionel Jacobs, M.D., Los Angeles.

12:00—**Business Meeting.**

MONDAY, MARCH 17 2:00 p.m.—Wilshire Room

Pain in Neuromuscular Skeletal Conditions

Second Session

Moderator: Bernard J. Michela, M.D., Long Beach

2:00—**Shoulder Pain—Evaluation and Treatment**—Sedgwick Mead, M.D., Vallejo.

2:50—**Recess.**

3:00—**Sensory Conduction and Pain of the Hands**—James G. Golseth, M.D., Pasadena.

PREVENTIVE MEDICINE AND PUBLIC HEALTH

Chairman............WILLIAM A. DEFRIES, M.D., FRESNO
Secretary............ALLEN C. NEISWANDER, M.D., WHITTIER
Assistant Secretary............GLEN W. KENT, M.D., MARTINEZ

MONDAY, MARCH 17 **2:00 p.m.—Colonial Room**

Preventive Medicine: You Ain't Seen Nothing Yet

Moderator: William A. DeFries, M.D., Fresno

2:00—**Preventive Medicine, Present and Future**—William A. Stewart, M.D., Washington, D.C., by invitation.

2:30—**Prevention: Its Role in Private Health and Public Medicine**—Lester Breslow, M.D., Los Angeles.

3:00—**The Patient: A Statistic or a Person**—Roger O. Egeberg, M.D., Los Angeles.

3:30—**Break.**

3:45— PANEL DISCUSSION

Members of the Panel: William A. Stewart, M.D., Washington, D.C., by invitation; Lester Breslow, M.D., Roger O. Egeberg, M.D., Paul F. Wehrle, M.D., and Joseph F. Boyle, M.D., all from Los Angeles.

4:45—**Break.**

4:50—**Business Meeting.**

PSYCHIATRY AND NEUROLOGY

Chairman (On Sabbatical)..HOWARD S. BARROWS, M.D., LOS ANGELES
Acting Chairman....HERBERT E. VANDERVOORT, M.D., SAN FRANCISCO
Secretary............SYDNEY H. POMER, M.D., LOS ANGELES
Acting Assistant Secretary............MORTON K. RUBINSTEIN, M.D., LOS ANGELES

MONDAY, MARCH 17 **9:30 a.m.—Oval Suite A**

Chairman: Morton K. Rubinstein, M.D., Los Angeles

9:30—**Recent Advances in Cerebrovascular Disease** — J. Carroll Ramseyer, M.D., Los Angeles.

10:15—**Recent Concepts in Multiple Sclerosis**—Norman S. Namerow, M.D., Los Angeles.

11:00—**Headaches: Current Diagnostic and Therapeutic Concepts**—Edwin L. Williams, Jr., M.D., Los Angeles.

12:00—**Business Meeting.**

MONDAY, MARCH 17 **2:00 p.m.—Oval Suite A**

2:00—**Social Disability: A New Therapeutic Focus**—Carroll M. Brodsky, M.D., Ph.D., San Francisco.

2:45— **Crisis Counselling**

PANEL DISCUSSION

Moderator: Sydney H. Pomer, M.D., Los Angeles

2:45—**Principles of Crisis Counselling as Illustrated by:**

Threatened Suicide—Norman D. Tabachnick, M.D. Los Angeles.

Counselling Today's Teenagers—Alexander R. Rogawski, M.D., Los Angeles.

Acute Marital Crisis—Edwin F. Alston, M.D., San Francisco.

The Seductive Patient — Herbert E. Vandervoort, M.D., San Francisco.

RADIOLOGY

Chairman............RICHARD P. STORRS, M.D., LOS ANGELES
Secretary............H. JOACHIM BURHENNE, M.D., SAN FRANCISCO
Assistant Secretary............MATHEW E. O'KEEFE, JR., M.D., WHITTIER

SUNDAY, MARCH 16 **9:30 a.m.—Colonial Room**

9:30—**Radiologic Diagnosis of Diseases of the Hand** — Lionel D. Ginsburg, M.D., Long Beach.

9:50—**Jugular Venography**—Richard M. Witten, M.D., Los Angeles.

10:10—**Neonatal and Congenital Diseases of the Portal Circulation**—J. Rosch, M.D., Prague, Czechoslovakia, by invitation.

10:40— **The Selection of Patients and Procedures for Diagnosis of Cerebrovascular Disease**

SYMPOSIUM

Moderator: William N. Hanafee, M.D., Los Angeles

Members of the Panel: Clark H. Millikan, M.D., Rochester, Minn., by invitation; Robert D. Bloodwell, M.D., Houston, by invitation; Julius Grollman, M.D., by invitation, and Gabriel H. Wilson, M.D., both Los Angeles.

12:10—**Business Meeting.**

SUNDAY, MARCH 16 **2:00 p.m.—Colonial Room**

Third Annual L. Henry Garland Memorial Lecture

Sponsored by the California Radiological Society

2:00—**Introduction**—G. Melvin Stevens, M.D., Palo Alto President, California Radiological Society.

2:05—**New Concepts in Cancer Control—Preventable and Avoidable Cancers** — Wendell G. Scott, M.D., St Louis, by invitation.

3:00—**Recess.**

3:15—**Annual Meeting of the California Radiological Society.**

UROLOGY

Chairman..Robert O. Pearman, m.d., Encino
Secretary..............................Milton Rosenberg, m.d., San Francisco
Assistant Secretary..................Robert A. C. Bridge, m.d., San Diego

MONDAY, MARCH 17 **9:00 a.m.—Gold Room**

9:00—**Chairman's Address: Significance of the Section on Urology of the CMA**—Robert O. Pearman, M.D., Encino.

9:15— **Current Practices in Urology**

Professors' Panel Discussion

Moderator: Robert O. Pearman, M.D., Encino

9:15—**Summary of Experiences with Renal Transplantation**—Donald C. Martin, M.D., University of California, Irvine.

9:45—**The Pathogenesis and Clinical Management of Urinary Calculi**—R. F. Gittes, M.D., University of California, Los Angeles, by invitation.

0:15—**Urinary Infection—The Portal of Entry**—Thomas A. Stamey, M.D., Stanford University.

0:45—**Recess.**

1:00—**The Catheter—Avoidance and Its Proper Use** — Robert J. Prentiss, M.D., University of California, San Diego.

11:30—**Problems of Diagnosis and Treatment in Pediatric Urology**—Willard E. Goodwin, M.D., University of California, Los Angeles.

MONDAY, MARCH 17 **2:00 p.m.—Gold Room**

Radiology in Urology

Professors' Panel Discussion

Moderator: Robert O. Pearman, M.D., Encino

2:00—**Renal Mass Lesions—Arteriography and Cyst Puncture**—John M. Riley, M.D., University of California, San Diego.

2:30—**Intravenous Pyelographic Evaluation for Hypertension—Criteria—Overall Accuracy**—James W. Lecky, M.D., University of California, Los Angeles.

3:00—**Cineradiography—Tape Recording with Image Intensifier—A Teaching, Diagnostic and Research Tool in Urinary Tract Physiology** — Melvin B. Rotner, Cmdr., MC, USN, San Diego, by invitation.

3:30—**Recess.**

3:45—**Business Meeting.**

4:00—**Urological Medical Economics—Pending Legislation**—Samuel G. Peck, M.D., San Diego.

4:30—**Should the Urology Section of the CMA Have a Voice in Sacramento and Washington—How Should It Be Arranged?**—Harold Kay, M.D., Oakland.

SCIENTIFIC AND ORGANIZATIONAL EXHIBITS

Ballroom, Casino Floor

A Community Need: Sex Education — Whose Responsibility? — Allen C. Neiswander, M.D., Whittier. This exhibit will illustrate the need for sex education by identifying indices of social disorganization, such as rates of unwed pregnancy, venereal disease rates, divorce and abortion. Suggestions will be given on how these needs can be met, with an emphasis on the physician's role.

The Margin of Safety of an Injectable Tranquilizer — Joseph C. Janis, M.D., Imola. The margin of safety, or therapeutic index, of a drug is the ratio of the Toxic Dose (at which 50 percent of the patients must be discontinued from the medication or have the dose reduced) to the Effective Dose (at which 50 percent of the patients receive benefit). This factor was given special attention in a double blind study of an injectable tranquilizer, fluphenazine enanthate, in sixty chronic schizophrenic women at the Napa State Hospital. Favorable reactions to the active medication were significantly better compared with the responses to an inert placebo. The technique of the study included a progressive increase in the dosage and in lengthening the time interval between injections. Side effects occurred, as expected, but more than had been anticipated in those who were older or had been ill longer. The exhibit will describe a step-by-step method, based on this experience, by means of which the general practitioner can readily and effectively titrate the correct doses for a course of treatment, especially in a chronic schizophrenic patient, and keep the side-effects down to a minimum.

The Problems of Drug Utilization — Norman DeNosaquo, M.D., Chicago, by invitation. This exhibit familiarizes physicians with the problems of drug utilization, including adverse reactions and the educational material available on this subject through the American Medical Association Department of Drugs. The exhibit will cover reactions in different specialty areas such as allergy, pediatrics and dermatology.

FDA's Adverse Drug Reaction Reporting Program — Miss Barbara Van Schoick, Washington, D.C., by invitation. The purpose of this exhibit is to encourage the reporting of adverse drug reactions — "drug experiences" — to the Food and Drug Administration. This theme is first developed by the presentation entitled, "Wanted: Your Drug Experience," which stresses that the prescribing physician should weigh the therapeutic benefits derived from drugs against their possible hazards. This presentation is followed by a description of how the FDA utilizes drug experience reports, emphasizing the return of urgent information to the practicing physician.

D.A.R.E. (Drug Abuse Research and Education) Presents a "Happening" — J. Thomas Ungerleider, M.D., Los Angeles. Through the sights and sounds of *today's youth,* this exhibit will show some of the ways in which teenagers are making an important contribution to our society and towards correcting the problem of adolescent drug abuse. There will be a filmed presentation dealing with difficulties in *adult-teenager communication,* especially focused on drugs; recorded songs which refer to drugs; a presentation on psychedelic art; and other illustrations of D.A.R.E. activities.

California Committee on Regional Medical Programs — Paul D. Ward, San Francisco, by invitation. The exhibit will consist of free-standing panels describing Regional Medical Programs in general terms, with pamphlets, brochures and other informational material available describing in detail past, present and future activities.

University of Southern California School of Medicine — Ralph M. Milliken, M.D., Los Angeles. A display relating to the school, its alumni and support groups, demonstrating its activities and available services.

The Prevention of Diseases due to Overcrowding, Undernourishment, Poverty and Ignorance: A New Approach —Louis Shattuck Baer, M.D., F.A.C.P., Burlingame. The exhibit will consist of presentations on the cause of overcrowding, poverty and ignorance; the recommended "new approach"; analysis of one thousand responses to this approach covering people of both sexes, of every age religion, race, occupation, financial status and politica opinion; and opinions of recognized authorities in the field.

Iron Deficiency in the United States — Miss Mary Jane Kibler, Chicago, by invitation. A brief review of iron requirements and the nature of iron deficiency in man i presented. It is pointed out that iron deficiency is high in frequency in infants and pregnant women, particularly when sensitive measurements such as plasma iron and iron binding capacity are employed for detection The difficulty of ensuring an adequate iron supply becomes apparent when daily iron requirements are translated into recommended dietary intake for iron. Th exhibit concludes that further studies are urgently needed to define more clearly the incidence of iron deficiency in the United States, to clarify further the availability of food iron and the actual dietary iron intake of the population, and, finally, to determine in the male the safe upper limits of iron supplementation to the diet.

edestrian and Cyclist Visibility: A Major Problem—The Use of Retro-Reflective Material — Fredric D. Burg, M.D., Cincinnati, by invitation. This exhibit, presented by the Department of Health, Education, and Welfare's National Center for Urban and Industrial Health, will show by means of a dark chamber how effective various materials are; a large selection of various types of retroreflectorized materials; and a review of statistics on pedestrian accidents.

rganic Impotence: Treatment by Implantation of Penile Prosthesis — R. O. Pearman, M.D., Encino. A study of etiology of organic impotence; anatomy of the phallus; development of silastic implant for correction, and results of this procedure in forty cases.

Electrocapacitance Plethysmography — William J. LaJoie, M.D., Los Angeles, by invitation. The exhibit will consist of capacitance plethysmography cuffs, a capacitance plethysmography calibrator and a capacitance detector and amplifier. It will include photographs of equipment, photographs and descriptions of techniques used, actual recordings, and also a brief history and the application of plethysmography. A live demonstration will be given to interested physicians.

Disability Benefits Under Social Security — Benjamin Lieberman, M.D., Oakland. This exhibit gives information regarding the Social Security Disability Benefit Program, including statistics regarding the recipients and their impairments.

Pacemakers — Medical Research Association of California —The exhibit will consist of an electrocardiogram of abnormal heart, showing slow beat; an electrocardiogram showing a "paced" heartbeat; an outline of the body with pacemaker in position and blinking lights showing heart rhythm; and an X-ray showing implanted pacemaker.

TELEVISION PROGRAMS

MARCH 16-19, 1969

West Venetian Room and West Venetian Foyer

Live Color Television from University of California, Los Angeles, will be presented in the mornings in the West Venetian Room; and Television-Videotape Demonstrations arranged by University of California, Los Angeles, University Extension, will be presented in the afternoons in the West Venetian Room Foyer.

Live Programs From
UCLA CENTER FOR HEALTH SCIENCES

Program Arrangements by
THE COMMITTEE ON TELEVISION

Donald G. Mulder, M.D., Chairman, Los Angeles
C. Gordon Frank, M.D., Los Angeles, by invitation
William J. Dignam, M.D., Los Angeles
Donald B. Rochlin, M.D., Los Angeles

and

Television-Videotape Demonstrations
THE MEDICAL TELEVISION NETWORK

UCLA, University Extension
Donald Brayton, M.D., Los Angeles
Richard R. Getz, Los Angeles, by invitation
David E. Caldwell, Los Angeles, by invitation
Richard S. Scott, M.D., Los Angeles, by invitation

The programs are subject to change, depending upon the availability of cases.

SUNDAY, MARCH 16 9:00 a.m.—West Venetian Room

9:00— DIAGNOSIS AND MANAGEMENT OF MASSES OF THE HEAD AND NECK

Moderator: Paul Ward, M.D., Los Angeles, by invitation

Panel: Mario J. Acquarelli, M.D., Los Angeles, by invitation; Herbert Dado, M.D., San Francisco, by invitation; and Max K. Pierce, M.D., Los Angeles.

Demonstrators: Walter Dishell, M.D., and Robert Sorosky, M.D., Los Angeles, both by invitation.

Tests and procedures will be demonstrated on actual patients.

10:30— BREAST CANCER: NEW TECHNIQUES IN DIAGNOSIS AND TREATMENT

Moderator: Wiley Barker, M.D., Los Angeles

Panel: Victor Richards, M.D., San Francisco, Andrew H. Dowdy, M.D., Los Angeles, and Louis J. Zeldis, M.D., Los Angeles.

Tests and procedures will be demonstrated on actual patients.

Noon—West Venetian Room Foyer

Noon-2:00 p.m.— VIDEOTAPE DEMONSTRATIONS

MONDAY, MARCH 17 9:00 a.m.—West Venetian Room

9:00— THE UNDIAGNOSED LUNG LESION

Moderator: James V. Maloney, Jr., M.D., Los Angeles

Panel: To be announced.

Surgeons: To be announced.

Operation: Pulmonary Resection.

10:30— DETECTION OF EARLY CERVICAL CANCER

Moderator: J. George Moore, M.D., Los Angeles, by invitation

Panel: Dean Moyer, M.D., Torrance, by invitation; William A. Manson, Jr., M.D., Pasadena, and Robert G. Good, M.D., Los Angeles.

Demonstrations and Surgical Procedures: (1) Vaginal Cytology, Colposcopy, Four Quadrant Biopsy, and Endocervical Curettage; (2) Cervical Conization—Leo Lagasse, M.D. and Charles R. Brinkman III, M.D., Los Angeles, both by invitation.

The presentation will indicate the diagnostic and therapeutic procedures designed to manage the patient who has a positive Pap smear, no obvious lesion on the cervix and who so often has early cervical cancer. It is designed to present a logical series of diagnostic steps and to indicate the pitfalls accruing from deviating from the diagnostic sequence.

TUESDAY, MARCH 18 10:00 a.m.—West Venetian Room

10:00— CORONARY ARTERY DISEASE: MEDICAL AND SURGICAL MANAGEMENT

Moderator: William P. Longmire, Jr., M.D., Los Angeles

Panel: Julius Grollman, M.D., and Rex MacAlpin M.D., Los Angeles, both by invitation; and William E. Bloomer, M.D., Los Angeles.

Surgeon: C. Gordon Frank, M.D., Los Angeles, by invitation.

Operation: Internal Mammary Implant for Revascularization of the Myocardium.

Noon—West Venetian Room Foye

Noon-2:00 p.m.— VIDEOTAPE DEMONSTRATIONS

WEDNESDAY, MARCH 19 **Noon—Foye**
West Venetian Roo

Noon-2:00 p.m.— VIDEOTAPE DEMONSTRATIONS

MOTION PICTURE PROGRAM

West Venetian Room Ambassador Hotel

Co-Chairmen:
Richard E. Gardner, M.D., San Francisco
W. Morris H. Noble, M.D., San Francisco

Five film symposia will be presented, each utilizing about two-thirds of the time for projecting of films, and one-third for discussion, questions and answers.

SUNDAY, MARCH 16 2:00 p.m.—West Venetian Room

2:00— SURGERY

Moderator: Richard E. Gardner, M.D., San Francisco

Discussants: Wiley F. Barker, M.D., Leonard Rosoff, M.D., Josiah Brown, M.D.; and by invitation Michael Bilitch, M.D., and Daniel H. Simmons, M.D., all from Los Angeles.

2:00—**Introduction.**

1. **Surgery of Primary Aldosteronism** — Richard H. Egdahl, M.D., Boston.

Methods for the diagnosis and localization pre-operatively of aldosterone-secreting tumors will be discussed. The techniques of both the anterior and posterior approaches to the adrenals will be demonstrated and reasons given for author's preference for the posterior approach if the side of the tumor has been determined pre-operatively. 27 minutes.

2. **Intensive Care in Critical Illness** — Lawrence G. Hampson, M.D., and Fraser N. Gurd, M.D., Montreal, Canada.

The film outlines the scope and development of intensive care, and illustrates the specific methods used in the assessment and treatment of critically ill patients. 28 minutes.

3. **Tracheostomy and Mechanical Ventilation** — Lester R. Bryant, Jr., M.D., Ward O. Griffen, Jr., M.D., and J. Kent Trinkle, M.D., Lexington, Kentucky.

This film demonstrates the technique of mechanical support of ventilation including tracheostomy, respirators, blood gases, tracheal toilet, antibiotics, and alternating tracheostomy cuff pressure site. 26 minutes.

3:45—**Panel Discussion.**

MONDAY, MARCH 17 12:15 p.m.—West Venetian Room

12:15— LUPUS ERYTHEMATOSUS

Moderator: William A. Atchley, M.D., San Francisco

Discussants: Yale B. Bickel, M.D., Los Angeles, by invitation; and Edmund L. Dubois, M.D., Los Angeles.

12:15—**Introduction.**

Systemic Lupus Erythematosus—P. Miescher, M.D., New York City; L. Shulman, M.D., Baltimore; and Yannic Gueguen, M.D., Basle, Switzerland.

Premiere Showing—Systemic Lupus Erythematosus is a complex disease, the true nature of which has been obscure until recently. This film gives a good and up-to-date summary of information available at present. It deals with the clinical picture, the characteristic renal lesion made available by biopsy, and the hematologic findings especially the LE test. The immunologic changes are only now becoming better understood, some of it since immunofluorescence has been introduced. The same applies to the antileukocytic autoantibody, the involvement of the complement, the rheumatoid manifestations and the possibility of a genetic defect. These advances have helped to understand the vascular, serosal and joint lesions, and a variety of other manifestations that have contributed to make this disease difficult to understand and difficult to treat. 18 minutes.

12:35—**Panel Discussion.**

MONDAY, MARCH 17 2:00 p.m.—West Venetian Room

2:00— ADOLESCENT SUICIDE

Moderator: Richard S. Scott, M.D., Los Angeles, by invitation

Discussants: Norman L. Farberow, Ph.D., and Michael Peck, Ph.D., Los Angeles, both by invitation.

2:00—**Introduction.**

2:10—**Rick: An Adolescent Suicide**—Norman L. Farberow, Ph.D., and Michael Peck, Ph.D., Los Angeles.

A reconstructed investigation into the psychological background of a seventeen-year-old high school senior who takes his own life.

TUESDAY, MARCH 18 2:00 p.m.—West Venetian Room

2:00— STROKE

Moderator: W. Morris H. Noble, M.D., San Francisco

Discussants: Theodore L. Munsat, M.D., by invitation, and Morton K. Rubinstein, M.D., both from Los Angeles; and Grant Gwinup, M.D., Irvine, by invitation.

2:00—**Introduction.**

1. **Vertigo: Differential Diagnosis** — Wallace Rubin, M.D., New Orleans, William S. Fields, M.D., Dallas, and Robert J. Wolfson, M.D., Philadelphia.

The film details the procedures and techniques for performing an office examination of the patient with vertigo. Onset of vertigo is shown, with manifestations of dizziness, loss of balance, and tinnitus. The general practitioner is seen performing an examination of the patient to determine whether he has true vertigo and whether it is peripheral or central in origin. The Romberg and Gait tests for balance are shown and the optokinetic, positional and caloric tests for the measurement of nystagmus are demonstrated. 25 minutes.

(Continued on next page)

2. **Hypertension: The Challenge of Diagnosis**—Walter M. Kirkendall, M.D., and Richard E. Lee, M.D., New York City.

With art animation sequences, the film demonstrates the approach to diagnosis by posing two questions every physician must answer in evaluating patients with hypertension: "What is the cause?" and "What damage has it done?" The film emphasizes the importance of a careful history, physical examination, and selective laboratory procedures to determine whether a primary or curable form of hypertension is present. It shows the organs most commonly damaged, and considers drug treatment. 20 minutes.

3. **Cerebral Vascular Disease: The Challenge of Diagnosis**—American Heart Association.

This film stresses the importance of accurate differential diagnosis and uses a series of case histories to illustrate the methods involved. 30 minutes.

3:45—**Panel Discussion.**

WEDNESDAY, MARCH 19 9:00 a.m.—West Venetian Room

9:00— CANCER

Moderator: John E. Connolly, M.D., Irvine

Discussants: Franklin L. Ashley, M.D., Joseph R. Bateman, M.D., both from Los Angeles, and Martin Brotman, M.D., San Francisco.

9:00—**Introduction.**

1. **Hormone Therapy for Advanced Cancer**—B. J. Kennedy, M.D., Minneapolis.

Presents the current role of hormone therapy for disseminated, inoperable or recurrent cancer of the breast, endometrium and prostate. Favorable response is demonstrated, as well as therapeutic failure. Criteria are presented for selecting patients and for assessing responses. The film emphasizes the importance of planning the full sequence of various therapies at the time of initial treatment in order to secure maximum benefits from all major modalities: Surgery, radiation, chemotherapy and hormone therapy. 21 minutes.

2. **Subcutaneous Mastectomy with Augmentation: Immediate or Delayed**—Bromley S. Freeman, M.D., Houston.

The various techniques of subcutaneous mastectomy with immediate as well as delayed augmentation mammoplasty are presented. The avoidance of complications by conservatism, modest expectations, and use of standard delicate technique is emphasized. The results of primary augmentation and of staged augmentation are shown. 15 minutes.

3. **Clinical Applications for Gastroscopy, Intragastric Photography, and Gastric Biopsy**—Harry Barowsky, M.D., Giancarlo Buganza, M.D., and Lawrence Greene, M.D., New York City.

The ability to detect gastric pathology has been greatly enhanced by several advances in the use of fiber gastroscopy, gastric biopsy under direct cinegastroscopic vision, and intragastric photography. This film shows how these techniques have been employed to solve difficult problems in the diagnosis of gastric disease. Illustrations show how these modalities helped to distinguish benign from malignant ulcers, demonstrated lesions when they were too small to be diagnosed by x-ray, localized bleeding areas, and clarified the underlying pathology in antro lesions, chronic gastritis, and neoplasms. 21 minutes.

10:45—**Panel Discussion.**

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Prentiss, Robert J., San Diego ... 19

Ququndab, Paul, Irvine ... 12

Rall, Joseph E., Bethesda, Md. ... 11, 14
Ramseyer, J. Carroll, Los Angeles ... 18
Randall, Harriett B., Los Angeles ... 9
Rapaport, Elliot, San Francisco ... 14
Rapaport, Samuel I., Los Angeles ... 15
Ravenscroft, James W., San Diego ... 13, 15
Reed, Richard J., New Orleans ... 8, 16
Rees, Rees B., Jr., San Francisco ... 13
Reisner, Ronald W., Los Angeles ... 13
Richards, Victor, San Francisco ... 14, 22
Riggio, Joseph, Jr., Northridge ... 12
Riley, John M., San Diego ... 19
Robinson, Tom W., Newport Beach ... 9
Rochlin, Donald B., Los Angeles ... 22
Rogawski, Alexander S., Los Angeles ... 18
Rokaw, Stanley N., Irvine ... 12
Rosch, J., Prague, Czechoslovakia ... 18
Rosenbaum, David L., Los Angeles ... 14
Rosoff, Leonard, Los Angeles ... 23
Rotner, Melvin B., San Diego ... 19
Rubin, David, Los Angeles ... 17
Rubinstein, Morton K., Los Angeles ... 18, 23
Rulon, David D., Oakland ... 8, 16
Russell, Keith P., Los Angeles ... 13, 15
Ryan, E. J., Phoenix ... 14

Sack, Robert A., Los Angeles ... 13, 15, 17
Sampson, John J., San Francisco ... 15
Schneider, Arthur S., Duarte ... 14
Schneidman, Harold M., San Francisco ... 12
Scholtz, Jud R., Pasadena ... 13
Schwartz, George, Los Angeles ... 14
Scott, Richard S., Los Angeles ... 22, 23
Scott, Wendell G., St. Louis ... 9, 18
Seaman, Arthur J., Portland, Ore. ... 15
Sedgwick, Robert, Los Angeles ... 13, 17
Shapiro, Marvin J., Encino ... 9
Silverman, Alan G., Los Angeles ... 10
Simmons, Daniel H., Los Angeles ... 23
Singer, Morley M., San Francisco ... 12
Skoog, William A., Los Angeles ... 14
Smith, Robert H., San Francisco ... 12
Smith, Mansfield F. W., San Jose ... 16
Smythe, Vernon L., Los Angeles ... 16
Sorosky, Robert, Los Angeles ... 22
Soss, Thomas L., San Mateo ... 16
Stamey, Thomas A., Stanford ... 19
Stevens, G. Melvin, Palo Alto ... 9, 16
Stewart, William A., Washington, D. C. ... 18
Strahan, Ronald, Torrance ... 16
Sulzberger, Marion B., San Francisco ... 1
Sutton, Wilfred, Northridge ... 9

Tabachnick, Norman D., Los Angeles 18
Tappan, James, San Francisco 9
Taybi, Hooshang, Oakland 8
Tesman, B. L., Anaheim 11
Treanor, Walter J., San Francisco 11
Tuffanelli, Denny L., San Francisco 12

Urban, Jerome A., New York City 8

Valentine, William N., Los Angeles 14
Vandervoort, Herbert E., San Francisco 18
Volwiler, Wade, Seattle 10

Walton, Robert G., Modesto 13
Ward, Paul, Los Angeles 22
Wehrle, Paul F., Los Angeles 18
Weitekamp, William, Los Angeles 13, 15
Werner, Mario, San Francisco 16
Wheatley, Melvin E., Jr., Los Angeles 9
White, Irving L., Long Beach 16
Whitsell, Alice J., San Francisco 13, 17
Whitsell, Leon J., San Francisco 13, 17
Williams, Edwin L., Jr., Los Angeles 18
Wilson, Gabriel H., Los Angeles 18
Wilson, George T., Palo Alto 13
Wilson, J. Walter, Long Beach 13
Wilson, Warren A., Los Angeles 15
Wiltse, Leon Lamont, Long Beach 16
Wiseman, Daniel, Los Angeles 12
Witten, Richard M., Los Angeles 18

Zeldis, Louis J., Los Angeles 22
Zike, Kenneth Z., Torrance 14, 17

OFFICERS AND DELEGATES

General Officers

Malcolm C. Todd, Long Beach	*President*
Albert G. Miller, San Mateo	*President-Elect*
William F. Quinn, Los Angeles	*Speaker, House of Delegates*
Joseph F. Boyle, Los Angeles	*Vice-Speaker, House of Delegates*
Richard S. Wilbur, Palo Alto	*Chairman of Council*
Helen B. Weyrauch, San Francisco	*Secretary*
Malcolm S. M. Watts, San Francisco	*Editor*
Robert L. Thomas	*Executive Director*
Hassard, Bonnington, Rogers & Huber	*Legal Counsel*

House of Delegates

TOTAL DELEGATES (349)

DELEGATES EX-OFFICIO (74)

Malcolm C. Todd, Long Beach	President
Albert G. Miller, San Mateo	President-Elect
William F. Quinn, Los Angeles	Speaker, House of Delegates
Joseph F. Boyle, Los Angeles	Vice-Speaker, House of Delegates
Richard S. Wilbur, Palo Alto	Chairman of Council
Helen B. Weyrauch, San Francisco	Secretary
Malcolm S. M. Watts, San Francisco	Editor

COUNCILORS

Stanley A. Moore (1970)	First District
Frank C. Melone (1971)	Second District
Henry V. Eastman (1970)	Third District
M. M. Haskell (1971)	Office No. 1, Fourth District
Elmer F. Gooel (1969)	Office No. 2, Fourth District
Homer C. Pheasant (1970)	Office No. 3, Fourth District
Lewis T. Bullock (1971)	Office No. 4, Fourth District
Joseph P. O'Connor (1969)	Office No. 5, Fourth District
Marvin J. Shapiro (1970)	Office No. 6, Fourth District
George C. Andersen (1971)	Office No. 7, Fourth District
Jean F. Crum (1969)	Office No. 8, Fourth District
Frank A. Rogers (1970)	Office No. 9, Fourth District
Joseph F. Maguire (1970)	Fifth District
Ralph W. Burnett (1969)	Sixth District
Richard S. Wilbur (1970)	Office No. 1, Seventh District
John T. Saidy (1971)	Office No. 2, Seventh District
Albert G. Clark (1969)	Office No. 1, Eighth District
Roberta F. Fenlon (1970)	Office No. 2, Eighth District
Harold Kay (1969)	Office No. 1, Ninth District
William F. Kaiser (1970)	Office No. 2, Ninth District
E. Kash Rose (1970)	Tenth District
Thomas N. Elmendorf (1971)	Eleventh District
Forest J. Grunigen (1970)	Twelfth District
Charles J. Tupper (1969)	Scientific Board Representative

ELECTED DELEGATES (276)

Delegates	*Alternates*
ALAMEDA-CONTRA COSTA (20)	
Ackerman, Frederick	Adams, Robert
Anderson, Conrad E.	Barber, Thomas E.
Armstrong, James R.	Bassett, J. Brandon
Boysen, Edwin E.	Byers, Gilbert
Davis, Aaron E.	Cherry, Donald W.
Donald, William G., Jr.	Cohen, James I.
Eisenberg, Harold J.	Cook, Wallace H.
Goodman, Julien M.	Duffy, Charles C.
Holden, Herbert	Frost, Gordon
Hoskins, H. Dean	Goetsch, Carl
Hudson, Charles B.	Greist, Elwood C.
Juul, Clement O.	Kirk, Ralph
Kunkel, Peter	Martin, L. Robert
Lewis, Gwilyn B.	Miller, A. Donald
Neighbor, Jean E.	Morrison, J. Evans
Powell, Oscar M.	Plaut, Eric A.
Purcell, Edward F.	Richards, Dexter N.
Rihn, Richard J.	Ross, Joseph
Truman, Stanley R.	Stanten, Arthur
Twigg, Edward	Wiesinger, Warren E.
BUTTE-GLENN (2)	
Murphy, Franklin L.	Guernsey, C. Meredith
Ritter, Dale W.	Sears, Adrian R. M.
FORTY-FIRST (2)	
FRESNO (5)	
Argo, W. L.	Ginsburg, H. M.
Howard, Arthur F.	Kass, Robert
Millar, Max S.	Kirkegaard, Dale
Smith, Robb	Steinberg, Theodore
Snyder, L. J.	Wilde, N. John
HUMBOLDT-DEL NORTE (2)	
Loring, Theodore	Braafladt, H. J.
Smith, E. Kenneth	Bux, Donald E.

Delegates	*Alternates*
IMPERIAL (2)	
Jaquith, George	Ajalat, M. P.
Schoensee, Burke	La Chance, Raymond
INYO-MONO (2)	
Christenson, Donald L.	Baughman, John A.
	Jones, Milton R., Jr.
KERN (4)	
Day, Robert L.	Anderson, Gene
Osell, L. N.	Clark, M. Marlin
Strongin, Seymour	Reese, Thomas V.
Vaughan, J. E.	Spaulding, Keith W.
KINGS (2)	
Brookshier, R. W.	Barreiro, A. L.
Kerr, Edwin E.	Bean, Glenn M.
LASSEN-PLUMAS-MODOC-SIERRA (2)	
Bross, Willard S., Jr.	Batson, Wilbur
Quinn, William J.	
LOS ANGELES (91)	
Adams, Donald A.	Alexakis, Peter
Alter, Marvin S.	Anderson, James E.
Andersen, George C.	Anderson, Richard E.
Asher, Leonard M.	Barker, Donald E.
Attyah, Albert M.	Bernstein, Harold
Austin, R. Reed	Blake, Courtland A.
Axelrod, Bernard	Bleecker, Harry H., Jr.
Bailey, Wilbur	Bleifer, Daniel J.
Barber, Clifford A.	Botzbach, Henry A.
Beasom, Ralph D.	Breakstone, Gerald J.
Bills, Jack W.	Bruckner, Sherman H.
Blood, William	Casberg, Melvin A.
Bowen, Gordon T.	Cobb, Dudley M., Jr.
Boyle, Joseph F.	Coleman, Thomas J.
Brennan, John C.	Cronin, John F.
Briney, Allan K.	Dahlquist, Joseph G.
Buehler, George S.	Del Junco, Tirso

Delegates	Alternates
Bullock, Lewis T.	Dickerson, Donald E.
Campion, George M.	Edwardes, Arthur F.
Case, Walter G.	Erickson, James F.
Compton, Russell F.	Feinberg, Munish
Cope, Jerome A.	Fields, Albert
Crane, Jay J.	Fife, J. Kingsley
Donahue, D. W.	Fischer, Barton L.
D'Orazio, Edward	Fox, Saul L.
Dorn, Robert M.	Freeman, Gordon L.
Doyle, John B., Jr.	Freidin, Morris
Ellerbeck, Walter P.	Frick, William Oliver
Elshire, H. Donel	Furer, Stanford A.
Evans, Creed M.	Haines, Charles L., Jr.
Evashwick, George	Hardin, Byron
Feldman, David H.	Hoffman, Peter L.
Fitch, Donald R.	Horowitz, Samuel
Florea, Darwin	Horton, James W.
Ford, James H.	Howard, Sidney M.
Fox, James B.	Hull, Forrest E.
Fredericks, Robert E.	Husted, Russell M.
Goodwin, William E.	Kaminski, Kenneth L.
Halasey, Thomas	Kaspar, Friedrich H.
Hamel, Neal C.	Kaufmann, Bertram J., Jr.
Haskell, M. M.	Kearns, Walter M., Jr.
Hill, Harry E.	Kelley, Walter W.
Hoffman, Eugene F., Sr.	Kern, William H.
Hohl, Mason	Korn, Bernard J.
Hood, Robert T., Jr.	Latshaw, Charles W.
Horner, David B.	Lefevre, Timothy M.
Jacobs, Laurence L.	Lindesmith, George G.
Jones, Henry A.	MacKenzie, Ronald J.
Keltner, Mark R.	Marcus, Stanley
Kessler, Bruce J.	Martin, Walter P.
Ketcham, Burton E., Jr.	McCandless, Harrison
Kiddie, Thomas	McElwee, Charles B.
Kranzdorf, Charles D.	McLaughlin, Henry M.
Lau, Michael W.	Medler, David C.
Lopez, Charles J.	Meine, Emile L., Jr.
MacInnis, Douglas N.	Michels, Arthur G.
Mailman, Richard H.	Miller, Woodrow
May, Lewis H. V.	Murray, Gregory C.
McCleary, Jack E.	Newhouse, Robert M.
Miller, Richard D.	Nishizawa, Akira
Milliken, Ralph M.	Palmer, Robert H.
Morgan, Henry G.	Penka, Ernest J.
Murrieta, A. J., Jr.	Picklesimer, James C.
Neuenschwander, Robert S.	Rabens, Robert A.
Noguchi, Thomas T.	Rayman, Irving B.
Olch, David I.	Reeder, David H.
Ottalini, Guy Adams	Riffenburgh, Ralph S.
Parlour, Richard R.	Rubin, Henry J.
Payne, J. Howard	Rudy, Norman E.
Penn, Sidney W.	Ryerson, F. Stuart
Phares, Walter S.	Sakaguchi, Sanbo S.
Pheasant, Homer C.	Silver, Bernard B.
Pollack, John V.	Smiley, Douglas F.
Quinn, William F.	Stauffer, Floyd R.
Richards, Melvin	Sullivant, Richard A.
Rothenberg, Sanford F.	Summers, L. F.
Smith, Thayer A.	Tashma, Albert
Starr, Harvey E.	Taylor, William A.
Stragnell, Robert	Thom, John G.
Taw, Richard L.	Tudbury, Patricia B.
Trumbull, William E.	Veregge, Gerald S.
Turrill, Fred L.	Vogel, Philip J.
Wasserman, John M.	Wallen, E. Robert
Watson, Robert L., Jr.	Walter, LeRoy E.
Westerbeck, Charles	Weil, William S.
Wiater, Edward J.	Weiss, Benjamin J.
Woolington, Sam S.	Weiss, Murray J.
Wunderlich, Edwin E.	Wigton, John R.
Yates, Paul D.	Wong, Thomas A.
Zinn, Willard J.	Woolley, Morton M.

MARIN (4)

Delegates	Alternates
Ablin, Arthur R.	Manwaring, John
Costanza, David	Raney, Gus
Jaros, Duval	Tavel, Frank
McGee, John	White, A. Halnan

MENDOCINO-LAKE (2)

Delegates	Alternates
Roberson, B. B.	Joyce, Donald G.
Waring, William W.	Nicholson, Thomas A.

MERCED (2)

Delegates	Alternates
Anglin, John V.	Kreps, Roland
Faber, Dorian	Soderstrom, Edwin

MONTEREY (3)

Delegates	Alternates
Hull, Osman H.	Eldredge, Eugene E.
Klinefelter, Robert P.	Kandlbinder, A. F.
Turner, Joseph E.	Pulford, James H.

NAPA (2)

Delegates	Alternates
Brignoli, Walter H.	Ehrlich, Harry
Ledwich, Thomas W.	Murray, Dwight H., Jr.

ORANGE (14)

Delegates	Alternates
Altman, Richard F.	Bouchelle, McLemore
Ball, Dexter T.	Burrill, C. William
Carroll, Vincent P.	Donaldson, A. Norton
Gerrie, Wallace A.	FitzGerald, P. J.
Graham, Ralph E.	Geddes, David K.
Hawkins, G. William	Hastings, Charles M.
Kay, Fred M.	Kammerman, Richard F.
Martin, Walter H.	McFarland, Philip H.
Mosier, Laurance A.	Neu, Robert E.
Nielsen, David I.	Plows, Charles W.
Paul, Carl J.	Schneider, Shirley M.
Plumb, Hugh J., Jr.	Thompson, Arthur F.
Price, J. B.	Voge, Lyle C.
Stonestreet, Marshall	Wightman, Ardath H.

PLACER-NEVADA (2)

Delegates	Alternates
Morgan, D. L.	Becker, Bruce A.
Shamhart, H. William	Scheideman, Oliver H.

RIVERSIDE (5)

Delegates	Alternates
Abbott, Donald	Borak, Peter J.
Ivanoff, John C.	Kinney, William
Silver, Harrison E.	Lyons, John C.
Stone, H. H.	Nevins, John W.
Zweig, Robert M.	Pitchford, Clyde A.

SACRAMENTO (8)

Delegates	Alternates
Berg, John A.	Babich, John
Berman, A. E.	Fong, William
Cook, Orrin S.	Janushkowsky, Alex
Farley, James O.	O'Kane, Calvin R.
Lambert, Lewis	Quillinan, Robert
Martin, James	Reilly, Philip J.
Pope, Glenn A.	Shaffrath, Max
Terry, Daniel	Steinberg, Stuart

SAN BENITO (2)

SAN BERNARDINO (6)

Delegates	Alternates
Gibson, Thomas	Ballard, Ross L.
Halburg, Clarence T.	Carmack, Charles
Hendrickson, M. A.	Judd, Richard
Miano, Ben D. A.	Krikes, Nicholas P.
Sprague, Charles P.	Wake, Donald K.
Sterling, Allen F.	Wilson, Richard J.

SAN DIEGO (14)

Delegates	Alternates
Brumbaugh, Simon C.	Bartel, Robert M.
Carpenter, Walter F.	Cowell, William E.
Hippen, Robert L.	Dill, Donald
Hokr, William K.	Elliott, Gladden V.
Isenhour, Roger C.	Flaiz, John
King, Ralph M.	Heard, Jerome L.
Levy, Edward I.	Herrick, William C.
Messenger, Harold	Kirtland, Howard B.
Peck, Sam	Peabody, Homer D., Jr.
Plumb, Robert T.	Peck, J. Haddon A., Jr.
Rumsey, John M.	Reck, Lawrence E.
Tancredi, Chester	Tisdale, William
Telford, Joseph W.	Tullis, Richard H.
Youel, Milo A.	Wells, John J.

SAN FRANCISCO (20)

Delegates	Alternates
Baer, Charlotte C.	Barrios, Xavier O.
Bender, William T.	Bovill, Edward G., Jr.
Biskind, Gerson R.	Bryan, John R.
Bonfilio, Nicholas D.	Cohn, Bradford
Feldman, Sanford E.	Coleman, Arthur H.
Fullenlove, Tom M.	Cook, Robert E.
Gallagher, Donald M.	Erskine, John M.
Gibbons, Henry, III	Hopp, Eugene S.
Herzog, George K., Jr.	Kelley, Edward T.
Hurwitz, Samuel	King, Charles D.
Lee, Jane F.	Miller, Charles F.
Pillsbury, Philip	Noble, W. Morris H.
Rixford, Emmet L.	Pevehouse, Byron C.
Robinson, Saul J.	Salomon, Maurice S.
Saunders, John B. de C. M.	Scholten, Paul
Schaffarzick, Ralph W.	Sirbu, Abraham B.
Schaupp, John B.	Solari, Rafael A.
Schaupp, Willis G.	Tipton, Dale L.
Wayburn, Edgar	Webb, Eugene M.
Williams, A. Justin	Wellington, C. J.

SAN JOAQUIN (4)

Delegates	Alternates
Benn, James J.	Clark, Stanley A., Jr.
McNally, John	Morozumi, John
Salter, Robert K.	Talley, Robert
Williams, George	Wass, Warren

Delegates	*Alternates*
SAN LUIS OBISPO (2)	
Chambers, James R.	Cletsoway, R. W.
Fryer, Harry J., Jr.	Warren, L. H.
SAN MATEO (7)	
SANTA BARBARA (5)	
Blanchard, John P.	Dahlen, Gregory A.
McNiece, Kenneth	Dietrich, Sanford R.
Miles, Harold	Elam, Eldon
Rutten, R. John	Feldsted, E. T.
Ziemba, Joseph	Owens, Daniel E.
SANTA CLARA (14)	
Armstrong, Frederick S.	Bonar, Samuel
Boice, Clyde	Burnett, Robert
Clark, Dan W.	Corsiglia, Victor F., Jr.
English, Leo	Hake, Dexter H.
Fox, Leon P.	Houck, George
Giansiracusa, Frank	Lee, R. Hewlett
Grossman, Maurice	Munemitsu, Saylo
Kaufman, S. Fred	Nola, Vincent F.
Liston, Edward	Parker, Malcolm
McCort, James J.	Schade, Hugh
O'Neill, Robert J.	Upton, Hubert M.
Rowles, Donald	Vincent, Paul J.
Scarborough, C. Gerald	Whelan, Harry G.
Skillicorn, Stanley A.	Zoglin, Stanton
SANTA CRUZ (2)	
DePuy, J. L.	Berman, Irwin B.
Mills, Richard G.	Nelson, Carl
SHASTA-TRINITY (2)	
Martin, George A.	Jantzen, Roland R.
Polka, Michael G.	Keye, John, Jr.
SISKIYOU (2)	
Anderson, Robert L.	
Reynolds, Joseph W.	
SOLANO (2)	
Gullock, Alvin H.	Olson, William J.
Schmutz, M. A.	
SONOMA (3)	
Clary, David T.	Anderson, Raymond C.
Craven, Wayne M.	Butler, Robert H.
Dunn, William J.	Lones, Frank E.
STANISLAUS (3)	
Nelson, William	Bigelow, Wayne B.
New, David J.	Galbraith, Nicoll
Purvis, Robert	Pote, William W.

Delegates	*Alternates*
TEHAMA (2)	
TULARE (2)	
Goettle, James W.	Bingham, Gary P.
Lavers, George D.	Feldmayer, James E.
VENTURA (4)	
Hair, Charles M.	Mathews, Albert L.
Huff, W. Cloyce	Pallais, Armando
Moore, James W.	Sherrill, Glenn D.
Rulfo, Henry J.	Steniger, David H.
YOLO (2)	
YUBA-SUTTER-COLUSA (2)	
Heckman, John R.	Morton, James R.
Wright, Bayard A.	Wallace, Robert N.
EX-OFFICIO SCIENTIFIC BOARD (18)	
Belford, William W.	Halter, Bert L.
Bettman, Jerome W.	Hibbard, Lester T.
Blanchard, Leland B.	Stein, Justin J.
Brockman, Seymour J.	Wood, David A.
Dillon, John B.	
Goebel, James L.	
Goerke, L. S.	
Gonda, Thomas A.	
Grayson, Charles E.	
Hockwald, Robert S.	
Jones, Ellis W.	
Levan, Norman E.	
McCandless, Carl M.	
Meleyco, Leo N.	
Petit, Donald W.	
Richards, Victor	
Rubin, David	
Russell, Keith P.	

EX-OFFICIO PAST PRESIDENTS (22)

Peers, Robert A.	1935	MacDonald, Frank A.	1957
Molony, William R., Sr.	1942	West, Francis E.	1958
Schaupp, Karl L., Sr.	1943	Reynolds, T. Eric	1959
Cline, John W.	1947	Foster, Paul D.	1960
Askey, E. Vincent	1948	Bostick, Warren L.	1961
Kneeshaw, R. Stanley	1949	Wheeler, Omer W.	1962
Cass, Donald	1950	Sherman, Samuel R.	1963
MacLean, H. Gordon	1951	Doyle, James C.	1964
Green, John W.	1953	Teall, Ralph C.	1965
Morrison, Arlo A.	1954	MacLaggan, James C.	1966
Shipman, Sidney J.	1955	Morrison, John G.	1967

EX-OFFICIO HONORARY PAST PRESIDENT (1)

Murray, Dwight H.

House of Delegates • 1969 Annual Session

AGENDA

Embassy Room, Ambassador Hotel

Speaker .... William F. Quinn, Los Angeles
Vice-Speaker .... Joseph F. Boyle, Los Angeles
Secretary .... Helen B. Weyrauch, San Francisco

FIRST MEETING, Saturday, March 15, 1969

REGISTRATION—3 p.m.

MEETING STARTS—4 p.m. SHARP

1. Call to order.
2. Announcement of Reference Committees and Miscellaneous Announcements.
    (a) Committee on Credentials. (Delegates must register with the Committee.)
    (b) Reference Committee on the Reports of Officers, the Council, the Commissions and Standing and Special Committees. (Reference Committee No. 1.)
    (c) Reference Committee on Finance, to study and make recommendations to the House of Delegates on the budget, submitted by the Council and appropriate committees, and the amount of dues for the ensuing year. (Reference Committee No. 2.)
    (d) Reference Committee on Resolutions and New and Miscellaneous Business. (Reference Committee No. 3.)
    (e) Reference Committee (No. 3A) on Resolutions and New and Miscellaneous Business.
    (f) Reference Committee (No. 3B) on Resolutions and New and Miscellaneous Business.
    (g) Reference Committee on Amendments to the Constitution and Bylaws. (Reference Committee No. 4.)
    (h) Reference Committee on California Blue Shield Business.
3. Honored Guests.
    (a) Fifty-year Members.
    (b) Past Presidents.
    (c) Allied Health Groups.
4. Report of Committee on Credentials, and Organization of the House of Delegates—Roll Call.
5. Recognition of President of the Woman's Auxiliary to the CMA—Mrs. Robert J. Douds.
6. Address by President—Malcolm C. Todd.
7. Report of the President—Malcolm C. Todd.
8. Report of the President-Elect—Albert G. Miller.
9. Report of the Speaker and Vice-Speaker of the House of Delegates—William F. Quinn and Joseph F. Boyle.
10. Report of the Trustees of the California Medical Association—Malcolm C. Todd.
11. Report of Physicians' Benevolence Fund, Inc.—Malcolm C. Todd.
12. Report of the Secretary—Helen B. Weyrauch.
13. Report of the Editor—Malcolm S. M. Watts.
14. Report of the Executive Director — Robert L. Thomas.
15. Report of Legal Counsel—Hassard, Bonnington, Rogers & Huber.
16. Report of the Executive Committee—Malcolm C. Todd.
17. Report of the Council—Richard S. Wilbur, Chairman.
18. Report of California Blue Shield Trustees—Carl E. Anderson, Chairman, Board of Trustees.
19. Report of Commissions.
    (a) Commission on Medical Services—Arthur F. Howard, Fresno.
    (b) Commission on Public Agencies—William F. Kaiser, Berkeley.
    (c) Commission on Community Health Services—Marvin J. Shapiro, Encino.
    (d) Commission on Communications — Elmer F. Gooel, Beverly Hills.
    (e) Commission on Professional Welfare—George K. Herzog, Jr., San Francisco.
    (f) Judicial Commission—Francis E. West, San Diego.
    (g) Commission on Allied Health Professions and Services—Frank C. Melone, Ontario.
    (h) Commission on Hospital Affairs — John T. Saidy, San Mateo.
    (i) Scientific Board—Charles J. Tupper, Davis.
20. Reports of Other Committees.
    (a) Bureau of Research and Planning — Carl E. Anderson, Santa Rosa.
    (b) Role of Medicine in Society—Malcolm S. M. Watts, San Francisco.
    (c) Organization Review & Planning — Jean F. Crum, Downey.
    (d) Committee on Legislation — Dan O. Kilroy, Sacramento.
    (e) Finance Committee—Harold Kay, Oakland.
    (f) Medical Executives Conference—William Dochterman, Sacramento.
    (g) Delegates to the AMA—Eugene F. Hoffman, Sr., Los Angeles.
21. Old and Unfinished Business.
22. New Business.
23. Adjournment.

CALPAC REPORTS
Immediately Following the Opening Session
of the CMA House of Delegates

SECOND MEETING, Tuesday, March 18, 1969 at 3:00 p.m.

(To be recessed and reconvened at 9:00 a.m., Wednesday, March 19)

ORDER OF BUSINESS

1. Call to order.
2. Supplemental report of Credentials Committee—Roll Call.
3. Introduction of President-Elect of Woman's Auxiliary—Mrs. Edmund Mahon.
4. Address by President-Elect—Albert G. Miller.
5. Secretary's announcement of Council's selection of time and place for the 1970 Annual Session.
6. Election of Officers:
   - (a) President-Elect.
   - (b) Speaker.
   - (c) Vice-Speaker.
   - (d) Councilors (three-year terms):
     - (1) Fourth District—Office No. 2—Elmer F. Gooel, Beverly Hills (term expiring).
     - (2) Fourth District—Office No. 5—Joseph P. O'Connor, Pasadena (term expiring).
     - (3) Fourth District—Office No. 8—Jean F. Crum, Downey (term expiring).
       Fourth District—Los Angeles County.
     - (4) Sixth District—Ralph W. Burnett, Bakersfield (term expiring).
       Sixth District—Amador, Calaveras, Fresno, Kern, Kings, Madera, Mariposa, Merced, San Joaquin, Stanislaus, Tulare and Tuolumne Counties.
     - (5) Eighth District—Office No. 1—Albert G. Clark, San Francisco (term expiring).
       Eighth District—San Francisco County.
     - (6) Ninth District — Office No. 1 — Harold Kay, Oakland (term expiring).
       Ninth District — Alameda and Contra Costa Counties.
   - (e) Delegates to the American Medical Association:
     (Delegates and Alternates to the American Medical Association are elected for terms of two calendar years. The Delegates and Alternates to be elected at this meeting will serve for two calendar years starting January 1, 1970, except as otherwise noted.)
     - (1) Francis E. West, San Diego (term expiring).
     - (2) Samuel R. Sherman, San Francisco (term expiring).
     - (3) Albert G. Miller, San Mateo (term expiring).
     - (4) John M. Rumsey, San Diego (term expiring).
     - (5) Eugene F. Hoffman, Sr., Los Angeles (term expiring).
     - (6) Warren L. Bostick, Irvine (term expiring).
     - (7) Vincent P. Carroll, Laguna Beach (term expiring).
     - (8) Ralph C. Teall, Sacramento (term expiring).
     - (9) James C. Doyle, Beverly Hills (term expiring).
     - (10) Wilbur G. Rogers, Glendale (term expiring).
     - (11) Charles B. Hudson, Oakland (term expiring).
     - (12) (a) New Office—to serve one-year term commencing immediately—January 1, 1969 through December 31, 1969.
       (b) Two-year term commencing January 1, 1970.
   - (f) Alternates to the American Medical Association:
     (Terms of all incumbents expiring. All offices for two-year terms starting January 1, 1970, except as otherwise noted.)
     - (1) Laurance A. Mosier, Garden Grove (alternate to Francis E. West).
     - (2) George K. Herzog, Jr. San Francisco (alternate to Samuel R. Sherman).
     - (3) A. B. Sirbu, San Francisco (alternate to Albert G. Miller).
     - (4) Robert T. Hood, Jr., Van Nuys (alternate to John M. Rumsey).
     - (5) Joseph F. Boyle, Los Angeles (alternate to Eugene F. Hoffman, Sr.).
     - (6) Walter H. Brignoli, St. Helena (alternate to Warren L. Bostick).
     - (7) William F. Kaiser, Berkeley (alternate to Vincent P. Carroll).
     - (8) Robb Smith, Orange Cove (alternate to Ralph C. Teall).
     - (9) Herman H. Stone, Riverside (alternate to James C. Doyle).
     - (10) Ben D. A. Miano, San Bernardino (alternate to Wilbur G. Rogers).
     - (11) Robert L. Watson, Jr., Los Angeles (alternate to Charles B. Hudson).
     - (12) (a) New Office—To serve one-year term commencing immediately—January 1, 1969 through December 31, 1969.
       (b) Two-year term commencing January 1, 1970.
7. Election of California Blue Shield Trustees (three-year terms):

   Report of CMA Council as Nominating Committee.

   Incumbents, terms expiring:
   Carl E. Anderson.
   Ralph W. Burnett.
   Mr. Ransom M. Cook (ineligible for re-election).
   Carl Goetsch.
   M. M. Haskell.
   Gregory C. Murray (ineligible for re-election).

8. Announcements by Secretary.
   Council's nominations of members of Commissions and Committees. (For approval by the House of Delegates.)
9. Reports of Reference Committees:
   - (a) Report of Reference Committee No. 1 on Reports of Officers, the Council, Commission and Standing and Special Committees.
   - (b) Report of Reference Committee No. 2 on the Budget submitted by the Council and appropriate committees, and the dues for the ensuing year.
   - (c) Report of Reference Committee No. 3 on Resolutions and New and Miscellaneous Business.
   - (d) Report of Reference Committee No. 3A on Resolutions and New and Miscellaneous Business.
   - (e) Report of Reference Committee No. 3B on Resolutions and New and Miscellaneous Business.
   - (f) Report of Reference Committee No. 4 on Amendments to the Constitution and By-laws.
   - (g) Report of Reference Committee on California Blue Shield Business.
10. Unfinished Business.
11. New Business.
12. Presentation of Officers:
    President—Presentation of Plaque to President Malcolm C. Todd.
    President-Elect.
    Speaker.
    Vice-Speaker.
13. Approval of Minutes. (Committee to edit.)
14. Adjournment.

William F. Quinn, *Speaker*
Helen B. Weyrauch, *Secretary*

Constitutional Amendment

FOR ACTION IN 1969

One Constitutional amendment was introduced in the 1968 House of Delegates and, under the terms of the Constitution, must lie on the table until the next regular meeting of the House of Delegates.

This proposed amendment is shown here for the information of the membership. In addition, the proposed Constitutional amendment is required to be printed in two issues of California Medicine before it comes before the House of Delegates for action.

* * *

CHARTERS, ARTICLE I, SECTION 5

Constitutional Amendment 1-68 Committee 4

Introduced by: The Council

Resolved: That Article I, Section 5 of the Constitution of this Association be amended by deleting the language in parentheses, so that the section will now read:

Section 5.—Component Society Charters

Charters to component societies may be granted and revoked as hereinafter prescribed. (, subject to the limitation that only one charter may be outstanding at any one time in any county.)

(Notwithstanding the foregoing,) One charter may be issued to a component society that is not limited as to geographical area or which overlaps the area covered by one or more existing component societies.

ANNUAL REPORTS

Reports of officers of the California Medical Association and the financial statements usually presented in the preconvention number of California Medicine are this year grouped with others in the Preconvention Bulletin made available to Delegates and Alternates to the House of Delegates. Copies are available to members on request directed to Robert L. Thomas, Executive Director, California Medical Association, 693 Sutter Street, San Francisco 94102.

WOMAN'S AUXILIARY

Thirty-Ninth Annual Convention

MARCH 16 to 19, 1969

Headquarters: Ambassador Hotel, Los Angeles

Convention Chairman: Mrs. John R. Black

Convention Co-Chairman: Mrs. F. LeGrand Noyes

REGISTRATION: Lobby, Ambassador Hotel
Sunday, March 16—9:00 a.m. to 4:00 p.m.
Monday. March 17—8:00 a.m. to 4:00 p.m.
Tuesday, March 18—8:30 a.m. to Noon

SATURDAY, March 15—Pre-Convention

4:00 p.m.—Presentation of Mrs. Robert J. Douds, Auxiliary President, to CMA House of Delegates, Embassy Room, Ambassador Hotel. Doctors' wives are invited to attend.

SUNDAY, March 16

9:00 a.m.—Executive Committee Breakfast Meeting, President's Suite, Ambassador Hotel.

1:30 p.m.—Pre-Convention Board Meeting, room to be announced.

MONDAY, March 17

9:00 a.m.—Opening Session of House of Delegates, Embassy Room.

1:30 p.m.—Afternoon Session of House of Delegates, Embassy Room.

TUESDAY, March 18

9:00 a.m.—Final Session of House of Delegates, Embassy Room.

12:30 p.m.—Presidents' Luncheon and Fashion Show, honoring Mrs. Robert J. Douds, Mrs. Edmund Mahon, Past State Presidents, and CMA Advisory Board and wives, Cocoanut Grove.

3:00 p.m.—Presentation of Mrs. Edmund Mahon, Incoming Auxiliary President, to the CMA House of Delegates, Embassy Room.

WEDNESDAY, March 19—Post-Convention

8:00 a.m.—Post-Convention Board of Directors Meeting; Mrs. Edmund Mahon, President, presiding; room to be announced.

10:00 a.m.—Orientation Meeting; Mrs. Edmund Mahon, President, presiding; room to be announced. 1969-1970 State Board Members, District Councilors, County and District Presidents and Presidents-Elect. Incoming County and District Board Members are welcome.

HOSPITALITY CENTER—Room to be Announced.

Sunday, March 16—9:00 a.m. to 11:00 a.m.
2:00 p.m. to 4:00 p.m.
Monday, March 17—8:00 a.m. to 11:00 a.m.
2:00 p.m. to 4:00 p.m.
Tuesday, March 18—8:00 a.m. to 11:00 a.m.

MRS. ROBERT J. DOUDS, *President*

MRS. EDMUND MAHON, *President-Elect*

Technical Exhibits

The Ballroom, Sunset Room and Boulevard Room of the Ambassador Hotel will house the technical exhibits. This area is noted as outstanding for exhibit purposes and many exhibitors will present their products and services for members of the Association.

All exhibits and all products exhibited have been screened by a committee as a means of eliminating those which do not meet higher standards. The exhibitors agree to this procedure and agree that by this means each will be in good company.

Here in one area will be found the latest developments in drugs, equipment and services to aid the physician in his professional activities. All physicians are urged to visit the exhibits; meetings have been planned to allow ample time for this important activity. Your visit will not only help bring your own knowledge up to date; it will demonstrate to our exhibitors, who contribute so much to the success of the meeting, that we recognize and appreciate their fine cooperation.

Exhibits will be open from 9 a.m. to 5 p.m. each day, with an early closing on Wednesday.

ABBOTT LABORATORIES Booth 6
Chicago, Illinois

Abbott Laboratories will feature Normosol® solutions, the phycologic approach to I.V. fluids and Erythrocin®, an antibiotic of unparalleled safety and known bactericidal action against many common pathogens.

ALOE MEDICAL Booth 88
St. Louis, Missouri

ALTA-DENA DAIRY Booth 63
City of Industry, California

Stop by the Alta-Dena Dairy booth, where we are sampling Certified Pasteurized Homogenized and Certified Raw Milk. Taste the difference, produced clean, disease free, bacteria free, guaranteed safe through daily laboratory tests, by the Los Angeles County Milk Commission. Kefir, a cultured milk, medical reports indicate excellent reports in normalizing intestional function following antibiotic therapy. This cultured milk is seeded with the friendly bacteria Lactobacillus Acidolphilus, Lactobacillus Caucasicus and Lactobacillus Bulgaricus. The Los Angeles Milk Commission will make available their reports for your inspection and our representative will be happy to answer any of your questions.

APACHE OIL PROGRAMS, INC. Booth 82
Minneapolis, Minnesota

Oil and Gas Exploration Programs for high income individuals.

ARMOUR PHARMACEUTICAL CO. Booth 73
Chicago, Illinois

You are cordially invited to visit the Armour Pharmaceutical Company Booth. The latest product information and clinical studies for Chymoral-100 Tablets and Letter Tablets (Sodium Levothyroxine, Armour) will be featured.

ARNAR STONE LABORATORIES, INC. Booth 44
Mount Prospect, Illinois

Americaine Topical Anesthetic—20% dissolved benzocaine in a water-soluble base—ointment, suppositories and aerosol forms. Hazel-Balm—cooling, soothing witch hazel and emollient lanolin in aerosol form—provides a comforting "cushion of foam." Isoclor—oral nasal decongestant and bronchodilator—tablet, liquid and timesule forms, also the anti-tussive Isoclor expectorant. Sopor—Non-barbituate hypnotic sedative for gentle untroubled sleep. Particularly useful with geriatric patients.

ASTRA PHARMACEUTICAL PRODUCTS, INC. Booth 20
Worcester, Massachusetts

Information and descriptive literature pertaining to Xylocaine (lidocaine) and Citanest (prilocaine) local and topical anesthetics, and iron preparations Astrafer (dextriferron) for intravenous use and Jectofer (iron sorbitex) for intramuscular administration will be available at the Astra booth.

AUDIO DIGEST FOUNDATION Booth 97
Pacific Medical Equipment Co. Booth 97
Los Angeles, California

Audio-Digest Foundation (a non-profit subsidiary of the California Medical Association) gives the busy physician a timesaving tour through the best of some 600 current medical journals, plus the highlights of scores of national meetings. Time-proven, but still unique — these medical tape-recorded services are now offered in reel to reel tape and Phillips type cartridges — General Practice, Surgery, Internal Medicine, Obstetrics & Gynecology, Anesthesiology, Ophthalmology and Pediatrics.

Digest subscribers listen in their car, home or office. Carefully selected tape equipment for playing the Digests is offered at the convention by Pacific Medical Equipment Co.

AUTOMATED MANAGEMENT SYSTEMS Booth 67
Los Angeles, California

As the nation's leading company offering professional management services, we are currently handling accounts receivable for thousands of physicians, dentists and lawyers—all over the country. We're not only up-dating their business practices, but we're also saving them time and money along the way. Which is pretty nice, you must admit.

With AMS you'll find more time for productive and profitable work. Increase in-office efficiency and accuracy of record keeping. Increase office payments, have fewer "collection agency" accounts and debts.

In addition, we can provide the full spectrum of management services, including leasing your office ejquipment and automobile, lending and investments.

AYERST LABORATORIES Booth 23
New York, N.Y.

BACTI-LAB INC. Booth 105
Mountain View, California

Uro-Bacti-Lab plate is a novel, simplified diagnostic tool designed for the lab and office practitioner to detect the presence and establish appropriate treatment of urinary tract infections. Simultaneous determination of urine culture, colony count, bacterial identification and antibiotic sensitivity test preparation time is 45 seconds. Aerco is a custom-designed dual chamber incubator, the lower one being option for CO_2. Temperature is constant throughout.

BEVERLY MEDICAL SUPPLY CO. Booth 30
Burbank, California

Beverly Medical Supply Co. will show the latest items available for the Doctor's office.

New instruments, new disposable items, and the latest diagnostic equipment will be featured.

BIRTCHER CORPORATION, THE Booth 68
Los Angeles, California

BREON LABORATORIES INC. Booth 16
New York, New York

Breon Laboratories Inc. presents a full line of products for the care of patients with chronic obstructive pulmonary diseases. Included are Alevaire, Bronkometer, Bronkosol, Bronkotabs, Bronkolixir and Bronkephrine. Supplying a variety of formulas, dosage forms and actions, these products offer both prophylaxis and therapy, in chronic or acute conditions, to all ages. Breon personnel will gladly discuss specific products and therapies with you.

BRISTOL LABORATORIES Booth 7
Syracuse, New York

Bristol Laboratories' exhibit features Polycillin (ampicillin trihydrate). This member of the Bristol family of synthetic penicillins is the first oral penicillin bactericidal against a significant number of Gram-negative and full spectrum of penicillin G-sensitive Gram-positive pathogens.

BROWN PHARMACEUTICAL CO., THE Booth 41
Los Angeles, California

The Brown Pharmaceutical Company will exhibit the following: Android family of products, Geramine, Cerebro-Nicin, Lipo-Nicin, Ferro-Gent, Calphosan, and Glukor. Samples and literature will be available.

BURROUGHS WELLCOME & CO., INC. Booth 17
Tuckahoe, New York

You are cordially invited to visit us for information on our products and the newest developments from the research facilities of Burroughs Wellcome & Co.

Of particular interest at this meeting is Zyloprim brand Allopurinol which represents a totally new concept for the management of gout, uric acid nephropathy and calculi, and hyperuricemia due to neoplastic disease and/or its intensive treatment.

Zyloprim was first synthesized in Wellcome Research Laboratories here in Tuckahoe, New York, and is the first drug to be marketed which reduces the formation of uric acid at its source.

CARNATION CO. Booth 14
Los Angeles, California

CASS & JOHANSING Booth 61
Los Angeles, California

Representatives will be present to discuss approved County Medical Association Programs—Group Disability, Non-Cancellable Disability, Life and Accidental Death & Dismemberment.

In addition, assistance in complete insurance programming will be available.

CIBA PHARMACEUTICAL COMPANY Booth 45
Summit, New Jersey

COLE PHARMACAL CO., INC. Booth 77
St. Louis, Missouri

Cole Pharmacal Company, Inc. will feature its family of ACTIVE Bronchopulmonary Agents—Asminyl, Iso-Asminyl, and Iodo-Niacin. Helpful information on Banalg will also be available.

CONTOUR CHAIR Booth 72
Los Angeles, California

DAYLIN MEDICAL & SURGICAL SUPPLY INC. Booths 101 & 102
Los Angeles, California

DIAL RESEARCH AND DEVELOPMENT CENTER Booths 67 & 70
Chicago, Illinois

DYNAPOWER SYSTEMS CORP. Booth 94
Santa Monica, California

EMKO CO., THE Booth 55
St. Louis, Missouri

The Emko Company exhibits the first aerosol foam contraceptive. Emko Vaginal Foam has been professionally recommended for over seven years. It has a high level of effectiveness without side effects. Women appreciate its esthetic qualities.

Literature and samples of Emko Vaginal Foam and My Own Vaginal Deodorant Spray and Towelettes available at The Emko Company exhibit.

ENCYCLOPAEDIA BRITANNICA, INC. Booth 59
Chicago, Illinois

Encyclopaedia Britannica welcomes delegates to the California Medical Association. As part of the EB's 200th Anniversary, we have on display the great new edition of Britannica, Great Books of the Western World, the Replica, Perspective, etc.

Stop and inspect these products in Booth No. 59. They are available to the delegates at our convention offer.

FINANCIAL CONCEPTS, INC. Booth 64
Los Angeles, California

Financial Concepts, Inc. is a unique corporation specializing in individually tailored investment programs, tax shelters, personal financial management, and practice management for physicians and dentists. FCI provides a wide range of expert services with offices in San Francisco, Los Angeles, and Chicago.

FINLEY, CHARLES O., & CO., INC. Booth 4
Los Angeles, California

FLINT DIAGNOSTICS Booths 34, 35, 36
Morton Grove, Illinois

Featured will be Flint Laboratories' newly introduced Choloxin (sodium dextrothyroxine) which effectively lowers elevated serum cholesterol. Also featured will be Hu-Tet (tetanus immune globulin, human), the homologous tetanus antitoxin and Synthroid (sodium levothyroxine) indicated in hypothyroidism.

FULLER LABORATORIES, INC. Booth 87
Eden Prairie, Montana

Tucks Family of Products, including Tucks medicated pads, Tucks Take-Alongs, Tucks witch hazel Ointment, Cream and Cream HC for management of pruritus ani, hemorrhoidal and perineorrhaphy discomfort. Fuller Shield dressing used following anorectal surgery, and its companion, ARD butterfly-shaped anorectal dressing. Scopettes—Proctosigmoidoscopic swabs lint-free, holds shape wet or dry.

GEIGY PHARMACEUTICALS Booth 23
Ardsley, New York

INSTITUTE OF CHEMICAL ANALYSIS Booth 37
Glendale, California

MMPI-ICA Report

For the first time a reliable tool and practical method is available to physicians for assessing degrees of emotional stress and ability to cope, ranging from normal to frank psychiatric disorders. In two minutes your aide can give your patient instructions on how to complete MMPI true-false questionnaire. A few days after mailing the answer sheet (specimen) you receive a comprehensive understandable computer analysis. Test kits with Reference Guide will be supplied on request.

INTERNATIONAL PHARMACEUTICAL CORP. Booth 11
Warrington, Pennsylvania

Gly-Oxide Liquid—cleansing, antimicrobial oral solution to relieve pain, cleanse, debride and protect against secondary infection.

Debrox Drops—to save time and avoid instrumentation in ear wax removal.

DIA-quel Liquid—new, pleasant tasting antidiarrheal.

JANRUS RECORDERS CORP. Booth 49
New York, New York

You are cordially invited to visit the Janrus Recorders Corp. booth where our representatives will be happy to demonstrate and answer any questions regarding their full line of tape and cassette recorders and dictating equipment.

We feature the following brand name recorders: Ampex, Uher, Aiwa, Crown, Panasonic, Norelco, and Hitachi.

KEY PHARMACEUTICALS, INC. Booth 104
Miami, Florida

Key Pharmaceuticals, Inc., through its own research, developed a new and exclusive method of producing sustained-action tablets. By utilizing the developments of our research, Key has manufactured a number of products which produce sustained-action in treating chronic diseases.

We cordially invite you to visit our booth.

LEDERLE LABORATORIES Booth 39
Pearl River, New York

Lederle Laboratories is pleased to support the 1969 Annual Session of the California Medical Association by its presence at this meeting. Our trained representatives in Booth No. 39 will be glad to discuss our well-known brand-name drugs such as Declomycin® and Achromycin®, the world's foremost broad-spectrum antibiotics; Aristocort®, the widely known steroid; the trivalent poliovirus vaccine Orimune®; and our other products applicable to your practice. Information is also available on our many other services to medicine.

LOMA LINDA FOODS Booth 27
Riverside, California

Loma Linda Foods, one of America's oldest manufacturers of fiber-free hypoallergenic infant soy milk, will show evidence of the nutritional adequacy of the product Soyalac. Representatives will explain why it is unusual in that it does not settle out, is milk like in texture, and does not tend to raise infant's serum cholesterol. Uses for adult ulcer patients and in cholesterol-lowering diets will be discussed. Samples will be served and recipes presented indicating the versatility of the product in diets of those with milk allergies or who for other reasons need to eliminate dairy milk from their diet.

M.D. ELECTRONICS, INC. Booth 53
Burbank, California

Treadmill Stress Test Equipment—Office size, motorized, variable speed treadmill. Has test monitor, heart rate meter—solid state EKG with automatic paper drive timer. Special pre-cordial exercise cable — high frequency rejector filter. Total package equipment necessary for doing exercise EKG in the office or the lab.

MEAD JOHNSON LABORATORIES Booth 106
Evansville, Indiana

The Mead Johnson Laboratories' exhibit has been arranged to to give you the optimum in quick service and product information. To make your visit productive, specially trained representatives will be on duty to tell you about Vasodilan isoxsuprine hydrochloride, Gynorest dydrogesterone, and Mucomyst acetylcysteine.

MEDCAL PHARMACEUTICALS INC. Booth 38
Glendale, California

Products: Liqui-K, potassium gluconate; Anesprin, acetaminophen; Medlax, Senna and Dss (dioctyl sodium Sulfosuccinate).

MEDICAL ENGINEERING CENTER Booth 21
Newbury Park, California

MEDINA AIRCRAFT CO. Booth 18
Long Beach, California

Distributor of Piper Aircraft.

MERCK SHARP & DOHME Booth 12
West Point, Pennsylvania

The Merck Sharp & Dohme exhibit has been designed to supplement the physician's therapeutic armamentarium. Technically trained personnel are present to discuss the scope and variety of services offered.

NEISLER LABORATORIES, INC. Booth 26
New York, New York

NETTLESHIP COMPANY OF LOS ANGELES, THE Booth 43
Los Angeles, California

Administrators of Professional Liability, Group Income Protection, and Life Insurance Programs for County Medical Associations and Trusts in California.

Qualified representatives available to discuss problems pertaining to hospital or individual professional liablity coverage, income protection, life or other types of insurance.

Literature which will assist in the prevention of claims and various forms to be used to protect, as far as possible, against malpractice claims.

NEUTROGENA CORP. Booth 75
Santa Monica, California

Neutrogena is a safe, transparent, extremely water soluble soap containing no free alkalai. Not a detergent, nor a medicated bar. This unique soap was granted patents in the U.S. and other countries (U.S. Pat. 820768). It is a safe adjunct to any regimen you prescribe. It does nothing . . . but clean.

ORGANON INC. Booth 81
West Orange, New Jersey

Durabolin® (nandrolone phenpropionate) patient anabolic therapy for weekly injection. Deca Durabolin® (nandrolone decanoate) potent long-acting anabolic therapy for monthly injection. Hexadrol® (dexamethasone) for the treatment of Rheumatoid Arthritis; Acute Rheumatic Fever and Corticosteroid, responsive Dermatologic, Ophthalmologic and Allergic disorders. Pregnosticon® Slide Test—a two-minute test for pregnancy. Monosticon®—a two-minute test for Infectious Mononucleosis. Rheumanosticon®—a one-minute test for Rheumatoid Factor.

ORTHO PHARMACEUTICAL CORP. Booth 65
Raritan, New Jersey

Welcome to Booth No. 65 where Ortho is proud to present the most complete line of medically accepted products for the control of conception. Of special note are the most recent products of the Ortho Research Foundation—Ortho-Novum® 1 mg Tablets, Ortho-Novum 2 mg Tablets, Ortho-Novum SQ® Tablets, Ortho-Novum 1/80® 21 Tablets, Delfen® Contraceptive Cream and Delfen Contraceptive Foam.

Also on display will be our well known products for the treatment of various forms of vaginitis.

Your questions will be welcomed by our representatives.

PARKE, DAVIS & COMPANY Booth 84
Detroit, Michigan

Medical service members of our staff will be in attendance at our booth to discuss important Parke-Davis specialties which will be on display.

PASADENA RESEARCH LABORATORIES, INC. Booth 103
Pasadena, California

Pasadena Research Laboratories, Inc., is pleased to be able to greet the members of the California Medical Association in Booth No. 103 this year. We will be featuring our curban appetite control medication and E-Vital creme for various minor skin affectations.

PERSON & COVEY, INC. Booth 13
Glendale, California

Person & Covey, Inc. will be exhibiting products of particular interest to the Dermatologists, Allergists, Plastic Surgeons, and Ophthalmologists. Our representatives will be waiting to discuss these products with you and to answer any questions you may have.

PERSONAL PRODUCTS COMPANY Booth 92
Division of Johnson & Johnson
Milltown, New Jersey

POYTHRESS, WM. P. & CO. INC. Booth 10
Richmond, Virginia

The Poythress exhibit will feature Trocinate, a unique, direct-acting (musculotropic) antispasmodic drug, and the Mudrane combinations, established Poythress products for relief of bronchial asthma. Solfoton, Solfo-Serpine, Panalgesic and Synirin will also be featured. Your requests for literature and professional trial quantities are cordially invited.

RITTER EQUIPMENT CO. Booth 98
Rochester, New York

Increase your patient load . . . conserve your energy! Move up to power . . . Ritter power! Both the Models 75 and XL45 tables allow you to examine and treat at *your* comfort level, decreasing back strain and eliminating fatigue while you position your patients easily and quickly with *their* comfort in mind. Visit our booth and discover why we are the "power people."

ROBINS, A. H., CO. Booth 19
Richmond, Virginia

You are cordially invited to visit the Robins display and meet our representatives who will welcome the opportunity to discuss products of interest with you.

SANDOZ PHARMACEUTICALS Booth 40
Hanover, New Jersey

Sandoz Pharmaceuticals cordially invites you to visit our display at booth No. 40, where we are featuring Mellaril, Sansert Cafergot P-B, Fiorinal and Fiorinal with codeine.

Any of our representatives in attendance, will gladly answer questions about these and other Sandoz products.

SAUNDERS, W. B., CO. Booth 5
Philadelphia, Pennsylvania

Saunders will have on display a complete line of their medical books, including many new titles and new editions.

SCHERING LABORATORIES Booth 57
Union, New Jersey

Schering Laboratories invites you to visit their exhibit, Booth Space No. 57, where their representatives will be available to discuss with you any questions you may have on Valisone®, Etrafon®, Garamycin®, Celestone®, Soluspan® Injection, Drixoral®, Tinactin®, Afrin® or any other Schering product.

SEARLE, G. D., & CO. Booth 8
Chicago, Illinois

You are cordially invited to visit the Searle booth where our representatives will be happy to answer any questions regarding Searle Products of Research.

Featured will be information on Ovulen-21, Enovid, Aldactazide, Flagyl, Lomotil, Pro-Banthine and other drugs of interest.

SIERRA MEDICAL SALES Booth 83
Riverside, California

SMITH KLINE & FRENCH LABORATORIES Booth 24
Philadelphia, Pennsylvania

Featured will be our comprehensive oral diuretic, Dyazide, each capsule containing 50 mg of Dyrenium (brand of triamterene) and 25 mg of hydrochlorothiazide.

SMITH, MILLER & PATCH, INC. Booth 42
New York, New York

Smith, Miller & Patch, Inc. will feature a new non-barbiturate hypnotic, Somnafac: our enlarged hematinic line—Vitron-C Plus and Vitron-C; our specialty bowel regulator, Kondremul; and some of our ophthalmics, especially, Vasocidin.

SQUIBB, E. R., & SONS Booth 3
New York, New York

Members of the medical profession who search for better agents to prevent and treat disease are eager to learn of new products and improvement in products.

Since therapeutic advances are constantly being introduced to the professional market, much valuable product information is available. Your inquiries about the latest results of our research will be welcomed.

STACEY'S Booth 15
Palo Alto, California
Distributors of medical books from all publishers

Publishers of Medical Books in Print, a catalog of medical books from all publishers. Wholesale distributors for the following concerns: *Appleton-Century-Crofts, Wm. C. Brown Co., Blakiston, Butterworth, Delmar Publishers, Warren H. Green, Inc., Grune & Stratton, Hoeber, Lange Medical Publications, Lea & Febiger, J. B. Lippincott Co., Little Brown & Co., Macmillan, C. V. Mosby Co., Oxford University Press, G. P. Putnam's Sons. W. B. Saunders,* Science and Behavior Books, *Springer Publishing Co., Williams & Wilkins Co.,* Year Book Medical Publishers.

STUART DIVISION Booth 2
Atlas Chemical Industries, Inc.
Pasadena, California

A cordial invitation is extended to all members and guests attending this meeting to visit the Stuart Division booth. Trained representatives will be in attendance to answer your questions on our products: Sorbitrate, Mylanta, Dialose, and Dialose Plus.

SYNTEX LABORATORIES, INC. Booth 22
Palo Alto, California

Visit Booth No. 22 for prescribing information on Norinyl® 1+80, now available in convenient 21 and 28 day oral contraceptive regimens and packaged in the feminine, convenient and attractive Memorette® dispenser.

Booth 1

Synalar® (fluocinolone acetonide), the topical corticosteroid designed to meet specific dermatologic needs, will be featured at Booth No. 1. Synalar has set a new standard of success in the treatment of a wide range of inflammatory dermatoses.

A warm invitation is extended to all physicians attending this meeting to visit our booth and discuss the latest developments from Syntex research.

UPJOHN COMPANY, THE Booths 85 & 86
Kalamazoo, Michigan.

Professional representatives of The Upjohn Company are eager to contribute to the success of your meeting. They are here to discuss products of Upjohn research designed to assist you in the practice of your profession. They welcome your inquiries and comments.

USV PHARMACEUTICAL CORP. Booth 31
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KEY TO ABBREVIATIONS USED

(BRP)—Bureau of Research and Planning; (CMA)—California Medical Association; (CR)—Case Report; (Ed.)—Editorial; (I)—Information; (LE)—Letter to Editor; (MP)—Medical Progress; (MSC)—Medical Staff Conference; (N/N)—News and Notes; (Or.)—Original Article; (PE)—Page End; (PHR)—Public Health Report.

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